A double-blinded, placebo controlled clinical trial evaluating the efficacy of the Harpago and celery seed cream in mild to moderate degenerative joint disease of the knee.

by

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A dissertation submitted to the Faculty of Health in partial compliance with the requirements for the Master's Degree in Technology: Chiropractic at the Durban Institute of Technology.

I, Desigan Pillay do hereby declare that this dissertation is a representation of my own work in both conception and execution.

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Om Saravanabavahye Namah

DEDICATION

I dedicate this work to my parents.

Mum, it is through your immeasurable strength, love and sacrifice that I have accomplished all that I have over the last six years.

Pappa, thank you for giving me the opportunity in pursuing my career in Chiropractic, and for your unfailing support and encouragement.

I couldn't have done it without you!

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ABSTRACT

Objective. To determine the efficacy of the Harpago and celery seed cream in mild to moderate degenerative joint disease of the knee in terms of subjective and objective clinical findings.

Method. Double-blinded placebo controlled study with 60 human subjects diagnosed as having mild to moderate degenerative joint disease of the knee by clinical and radiographic examination. They were randomly divided into two groups of thirty individuals. One group received the Harpago and celery seed cream while the second group received the placebo (aqueous cream). Pain, physical function and range of motion of the involved knee were assessed over a two- week period.

Results. Both groups showed improvements in NRS ($p=0.063$) and PSFS scores ($p=0.153$, $p=0.525$, $p=0.122$) over the two-week period while, the active treatment group showed an overall statistically significant improvement in algometer readings ($p=0.004$) and, flexion ($p=0.002$) and extension ($p<0.001$) readings.

Conclusion. It was shown, that the Harpago and celery seed cream was a beneficial modality in the management of mild to moderate degenerative joint disease of the knee.

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CHAPTER 1

1.0 INTRODUCTION

1.1 THE PROBLEM AND ITS SETTING

Degenerative joint disease (DJD) is the most prevalent form of arthritis and is a major cause of disability in the elderly (Creamer and Hochberg, 1997). The site most commonly affected by DJD is the knee joint (Berman *et al.,* 1998), and according to Brandt *et al.* (1999) DJD of the knee results in more disability than any other joint affected by DJD.

In western countries, radiographic evidence of this disease is present in majority of persons by the age of 65 years and in about 80% of persons more than 75 years of age. Approximately 11% of persons over the age of 64 have symptomatic degenerative joint disease of the knee (Manek and Lane, 2000). In some people, evidence of degenerative changes may exist by the second or third decade of life usually without associated symptoms and by age 40, almost everyone has some degenerative changes in weight-bearing joints (hip and knee joints) and, by age 75, virtually everyone has changes in at least one joint (Cooper, 1998).

Pain is the most common symptom in patients with DJD, associated with the use of the joints. Other symptoms include joint stiffness, limitation of movement, variable degree of local inflammation, and loss of function (Yasmin *et al.,* 2000). A primary concern among patients with this disease is the threat/challenge of coping with chronic progressive pain. Pain combined with the anatomical impairment which is characteristic of knee DJD, results in significant physical disability. This is a particularly important consequence of knee DJD in that physical disability adversely affects patients' quality of life and increases the risk for both their morbidity and mortality (Rajeski and Shumaker, 1994). Persons with knee DJD report difficulty with walking, stair climbing, rising from a chair, transferring in and out of a car, and lifting and carrying, all of which are

necessary to maintain independence and good quality of life (Ettinger and Afable, 1994).

DJD is non-fatal, but incurable condition for which they are few effective treatments, symptoms of pain and physical disability can persist for long periods of time (Ettinger and Afable, 1994). Therefore, the goals of DJD therapy are to decrease pain and improve function (Lane and Thompson, 1997). Conventional non-surgical management of DJD is inadequate or inappropriate due to lack of efficacy or adverse medical reactions (Zizic *et al.*, 1995).

1.2 AIMS AND OBJECTIVES OF THE STUDY

The aims of this study was to evaluate the efficacy of the Harpago and celery seed cream regarding changes in pain and range of motion in mild to moderate DJD of the knee in terms of subjective and objective findings.

1.2.1 OBJECTIVE ONE

The first objective was to evaluate the efficacy of the Harpago and celery seed cream with respect to pain and physical function in mild to moderate DJD of the knee in terms of subjective clinical findings.

1.2.2 OBJECTIVE TWO

The second objective was to evaluate the efficacy of the Harpago and celery seed cream with respect to pain threshold and range of motion in mild to moderate DJD of the knee in terms of objective clinical findings.

1.3 HYPOTHESES

1.3.1 HYPOTHESES ONE

It was hypothesized that the Harpago and celery seed cream would be more effective than placebo in decreasing pain and improving subjective activity performance in subjects affected by mild to moderate DJD of the knee.

The null hypotheses (H_o) states that there would be no difference between the two treatment protocols in terms of decreasing pain and improving subjective activity performance in subjects affected by mild to moderate DJD of the knee.

The alternate hypotheses (H_a) states there would be a significant difference between the two treatment protocols in terms of decreasing pain and improving subjective activity performance in subjects affected by mild to moderate DJD of the knee.

1.3.2 HYPOTHESES TWO

It was hypothesized that the Harpago and celery seed cream would be more effective than placebo in improving knee range of motion and decreasing tenderness in subjects affected by mild to moderate DJD of the knee.

The null hypotheses (H_o) states that there would be no difference between the two treatment protocols in terms of improving knee range of motion and decreasing tenderness in subjects affected by mild to moderate DJD of the knee.

The alternate hypotheses (H_a) states there would be a significant difference between the two treatment protocols in terms of improving knee range of motion and decreasing tenderness in subjects affected by mild to moderate DJD of the knee.

1.4 MOTIVATION AND BENEFITS OF THE STUDY

There is no known cure for degenerative joint disease, and the goal of contemporary management of the patient with degenerative joint disease remains control of pain and improvement in function and health-related quality of life with avoidance, if possible, of therapeutic toxicity (NIH conference: 1999-no authors listed).

Traditionally, pharmacological treatment for DJD have been based on the use of non-steroidal anti-inflammatory drugs (NSAIDs), which can be expensive and can result in gastrointestinal (GI) toxicity, especially in elderly patients with DJD. Therefore, clinicians should consider other treatment options before initiating the use of NSAIDs (Lane and Thompson, 1997).

According to Gordon *et al.* (1998), patients with knee DJD who do not respond to standard pharmacological and non-pharmacological therapies and are not candidates for knee surgery may be candidates for other therapies.

According to the manufacturers of the Harpago and celery seed cream, it is a natural derivative for arthritic conditions with no known side effects (www.houseofhealth.com). It is a new product on the market for which no clinical trials have been conducted. Therefore, it was the researchers aim to evaluate its efficacy in the management of mild to moderate degenerative joint disease of the knee.

CHAPTER 2

2.0 REVIEW OF LITERATURE

2.1 INTRODUCTION

The following is an overview of the related literature concerned with the basic clinical, etiological and epidemiological aspects of degenerative joint disease of the knee. The theoretical basis for the action and effects of the Harpago and celery seed cream are discussed as well.

2.2 DEFINITION OF DEGENERATIVE JOINT DISEASE AND ITS SYNONYMS

Degenerative joint disease (DJD) is primarily a non-inflammatory disorder of movable joints characterized by an imbalance between the synthesis and degradation of the articular cartilage, leading to the classic pathologic changes of wearing away and destruction of cartilage (MerckMedicus Modules, 2001).

In this study, subjects with mild to moderate DJD of the knee were chosen. Although no formal definition of mild to moderate DJD exists, relevant review of the literature indicates it as persons with early radiographic changes of DJD i.e. non-uniform loss of joint space, subchondral sclerosis, osteophyte formation and joint swelling. Since loose body formation, joint subluxation and destruction with signs of ankylosis are seen with progression of the disease in the late stages (Swagerty and Hellinger, 2001), subjects who present with these signs were excluded as this would have altered the clinical outcomes with respect to knee range of motion and possibly pain.

DJD is also known by the terms degenerative arthritis, osteoarthritis/osteoarthrosis or degenerative arthrosis, but the term degenerative joint disease (DJD) has gained the most universal acceptance (Yochum and

Rowe, 1996). The original term osteoarthritis which is still currently used is misleading as it denotes an inflammatory disorder. DJD is not primarily an inflammation of joints but the inflammation may occur secondarily and play a role in disease progression (Burns and Kumar, 1999).

2.3 CLASSIFICATION OF DJD

DJD is classified as primary or idiopathic if the aetiology is unknown and secondary when degenerative joint changes occur in response to a recognizable or systemic factor (Nuki *et al.*, 1999); however secondary DJD is pathologically similar to primary DJD (Yasmin *et al.*, 2000).

The American College of Rheumatology (ACR) has developed a classification system for DJD:

- Idiopathic: Localized to one particular joint e.g. hands, feet, hips and other single sites or Generalized (three or more joints listed previously).
- Secondary: Post-traumatic, congenital or developmental diseases, localized (e.g. hip dysplasia), generalized (e.g. chondrodysplasias, inherited metabolic diseases, calcium-deposition disease), other bone and joint disorders (e.g. Avascular necrosis, Rheumatoid arthritis, Paget's disease).
- Other diseases: Endocrine diseases (e.g. Acromegaly, Hyperthyroidism), Neuropathic (Charcot's) arthropathy (Creamer and Hochberg, 1997).

Currently medical experts are of the opinion that primary OA probably does not exist, and that the mechanical deviation in the involved joint degeneration is the cause of very mild infantile and childhood disorders, such as congenital dysplasia, that were not observed at the time. Secondary OA results from either an abnormal concentration of force across an articulation (junction of two bones or surfaces) with normal articular cartilage matrix or a normal concentration of

force across an abnormal joint. As a result, secondary OA is often the result of injury (trauma) or repetitive motion such as found in certain occupations, but it can also result from congenital conditions and systemic disease. Secondary OA is more likely to show at an earlier age than primary OA, and if diagnosed early may be an initial clue to potentially dangerous and treatable systemic diseases (American Association of Orthopaedic Surgeons, 2003).

2.4 RISK FACTORS

2.4.1 AGE

Age is the strongest determinant of degenerative joint disease with prevalence rates for all joints rising with increasing age (Creamer and Hochberg, 1997). The mechanism by which age predisposes to DJD is unclear. It is tempting to speculate that biochemical changes within articular cartilage render it more susceptible to damage and degradation but evidence to support this is lacking (Creamer and Hochberg, 1997). The mechanism underlying these striking age associations might relate to the age-related reduction in vascular supply, nutrition of joint tissues or reduced regenerative potential of connective tissue. This might lower resilience to insult which may favor more rapid progression and poor outcome. There is certainly a dramatic decline with aging in the biomechanical properties of cartilage matrix, probably caused by the subtle but cumulative changes in the structure of collagens, proteoglycans and matrix proteins. The effect of aging on both normal and DJD tissues certainly deserves further study (Brandt *et al.*, 1998). According to Cooper (1998), autopsy studies report that cartilage erosions, subchondral reaction and osteophytes are present in the knees of 60% of men and 70 % of women who die in the seventh and eight decades of life. Local South African statistics were examined from five clinical trials on degenerative joint disease of the knee, which were conducted at the Durban Institute of Technology's Chiropractic Day Clinic. These studies revealed that of the 300 subjects included in these clinical trials, 80.4% of the subjects

ranged between the ages of 50 and 85 years while the remainder 29.6% ranged between the ages of 35 to 49 years (Fish, 2002; Robertson, 2001; Tucker, 2001; Nel, 2001 and Naidoo, 2001). The US Health Examination Survey for osteoarthritis of hands and feet found that radiographic hand osteoarthritis was present in less than 5% of individuals under age 35 and in more than 70% of those aged 65 or over (Rottensten, 2002).

2.4.2 SEX PREDISPOSITION

Women are at a higher risk of developing DJD than men, particularly after menopause (Creamer and Hochberg, 1997). Hart *et al.* (1999) stated that 3% of middle-aged women will develop new knee osteophytes and joint space narrowing each year, the susceptibility to these changes in older women is twice as great compared with those twenty years younger. Prior to the age of 50, knee DJD is more frequent in men, but after that age it is more common and the incidence increases more rapidly in women. This suggests that postmenopausal hormone deficiency may be a risk factor for DJD and therefore possible knee pain development in women (Nevitt *et al.*, 2001). The increasing prevalence of DJD with age, compounded by the greater life expectancy among women, results in DJD being twice as prevalent among women as among men age 55 years and older. These gender differences are most prominent when DJD affects the knee (7.3% of woman and 4.1% of men age 55 through 64 years, 18% of women and 8.3% of men age 65 through 74 years) (Brandt, 1995). According to local South African statistics mentioned previously, five clinical trials on degenerative joint disease of the knee were conducted at the Durban Institute of Technology's Chiropractic Day Clinic. These studies revealed that of the 300 subjects included in these trials, 53% of the subjects were female (Fish, 2002; Robertson, 2001; Tucker; 2001; Nel, 2001 and Naidoo, 2002).

2.4.3 ETHNICITY

An earlier study by Solomon *et al.* (1976) reported that in South Africa a lower prevalence of multiple joint involvement and of degenerative joint disease of the hands, feet and hips in black women compared with white women and a higher prevalence of hand degenerative joint disease in black men than in white men (Rottensten, 2002). Lately, according to the local South African studies previously mentioned, of 300 subjects included in those clinical trials, 80% were Whites, 16% were Indian, 2% were Black and 2% were Coloured (Fish, 2002; Robertson, 2001; Tucker, 2001; Nel, 2001 and Naidoo, 2001). However, these figures do not represent the total population. The exact incidence and prevalence of DJD in South Africa, has not been studied at a national level (Naidoo, 2001). Analysis of the National Health and Nutritional Examination Survey I data reveals that the prevalence of knee degenerative joint disease in the US, especially in women, is higher among Blacks than among Whites. Van Sasse and colleagues as cited by Rottensten (2002), compared radiological degenerative joint disease in a Dutch population with 10 other populations in the countries of Japan, the United States, Bulgaria, England and South Africa. They concluded that age-specific patterns of degenerative joint disease by site were similar across studies and that the differences existing between populations are differences in level for most joints; joints with a low prevalence of degenerative joint disease in one population are relatively degenerative joint disease-free in all populations. However, it has yet to be established whether these differences are real, or due to inter-observer variation, or to differences in genetics or the distribution of risk factors (Rottensten, 2002).

2.4.4 GENETICS

Reports by both, Palotie and colleagues and Knowlton and colleagues as cited by Spector *et al.* (1996), on three unrelated families demonstrated coinheritance of primary generalized DJD with specific alleles of the gene for Type II

procollagen (COL2A1) on chromosome 12, the precursor to cartilage protein. This was associated with a single base mutation of this allele in affected members of several families, all with evidence of an associated chondrodysplasia. Spector *et al.* (1996) further investigated female twin pairs between identical and non-identical, showed significant genetic predisposition correlations for radiographic features of DJD at the hand and knee. The intraclass correlation of total radiographic DJD score in identical pairs (*r*MZ) was 0.64 (SE 0.05) compared with 0.38 (0.08) in non-identical pairs. These results demonstrate a clear genetic effect for radiographic DJD of the hand and knee in women (Spector *et al.,* 1996). Although mutations in the gene for Type II collagen (COL2A1) have been associated with early polyarticular DJD with chondrodysplasia, it is unlikely that there is a single gene for a structural component of cartilage that fully explains the genetic contribution to degenerative joint disease (Creamer and Hochberg, 1997).

2.4.5 OBESITY

Obesity has been identified as a major risk factor for the development and progression of knee DJD. According to the Framingham study by Felson *et al.* (1995), it was reported that weight loss was associated with a slower rate of development of symptomatic knee DJD in women. McAlindon *et al.* (1996), report that a higher body mass index (BMI), in particular, is a potent risk for both patellofemoral (PF) and tibiofemoral (TF) patterns of knee DJD. Both patterns showed an association with increasing body mass index (BMI) and this relationship appeared stronger for PF than TF disease. These associations were even stronger for the combined pattern, particularly for BMI (highest vs. lowest tertile, p=0.0001) and knee injury (p=0.001).

Despite the significant risk imposed by obesity, the mechanism by which the excess weight influences disease onset and progression is unclear. Metabolic factors and increased biomechanical load across articular cartilage have been

postulated as possible disease inducing mechanisms (Powell *et al.*, 2005). Hart and Spector (1993) as cited by Powel *et al.* (2005), have suggested that metabolic factors are associated with obesity and OA. However, many studies have not supported a metabolic link in the pathogenesis of the disease. The National Health and Nutrition Examination which examined serum cholesterol, uric acid, body fat distribution and blood pressure among 3885 American adults aged 45–74, found no link between these metabolic factors and the association between obesity and knee OA (Powell *et al.*, 2005).

2.4.6 MECHANICAL DERANGEMENT

According to Creamer and Hochberg (1997), joint trauma is a major risk factor in developing DJD of the knee. Surgical removal of a meniscus following knee injury also represents a significant risk factor for radiographic tibiofemoral joint DJD (Roos *et al.*, 1998). Varus-valgus laxity may increase the risk of knee DJD and cyclically contribute to its progression (Sharma *et al.*, 1999). Any shift from a neutral hip-knee-ankle alignment alters load distribution; varus and valgus alignment increase medial and lateral compressive forces, respectively. Knee laxity results with abnormal displacement of the tibia in relation to the femur which shifts opposing surfaces of tibiofemoral contact so that the congruence is reduced and increases shear and compressive forces on the articulating surfaces (Sharma *et al.*, 2003).

2.5 PATHOGENESIS OF DJD

The aetiology of primary DJD is unknown. Many biochemical, inflammatory and immunological factors have been considered. These explanations can be placed into two broad categories: normal forces acting on abnormal cartilage with an inadequate healing response or excessive forces acting on normal cartilage. Several factors have been found to play a role in either the initiation of degenerative joint disease or its perpetuation. These include:

- Aging
- Alterations in the matrix structure of articular cartilage
- Activity of articular cartilage chondrocytes
- Chemical mediators in synovial fluid
- Trauma
- Poorly understood immune responses (Martin, 1994).

In the early stages, the cartilage is usually thicker than normal, but with progression of DJD, the joint surface thins and the cartilage softens, leading to disruption in the integrity of the surface and development of clefts. This results in the formation of ulcers that extend deep into the bones. Although repair of the cartilage does occur, the resultant repair is inferior and is unable to withstand mechanical stress. Cartilage is metabolically active. However, as stress on the joints continue, the cartilage becomes hypocellular or lacks the chondrocytes to help rebuild and maintain integrity. (Yasmin *et al.*, 2000)

2.5.1 ARTICULAR CARTILAGE

The essence of DJD is a non-inflammatory degeneration of articular cartilage and the clinical diagnosis of DJD depends on symptoms like pain, radiographic detection of joint space narrowing as a result of articular cartilage loss and in many cases the presence of osteophytes which occurs as a tissue repair response from progressive destruction of cartilage (Heinegard *et al.*, 1998).

A thin layer of cartilage called articular cartilage covers the subchondral bone in the knee joint. The articular cartilage is firmly attached to its underlying subchondral bone by a subchondral plate. This allows the subchondral plate to act as a shock absorber, which protects the joint from applied stresses. A thin layer of calcified cartilage separates the non-calcified or articular cartilage from its bony subchondral bed. The interface between the calcified cartilage and articular cartilage is known as the tidemark. The articular cartilage, with the

subchondral bone and the surrounding skeletal muscles, supports even distribution of weight loading across the entire joint structure. Articular cartilage has a milky, glass-like appearance and is composed of:

- extracellular matrix (ECM) (98-99% of total volume)
- chondrocytes (1-2% of total volume) (Keuttner and Thonar, 1998).

The ECM is made up of water, collagen (mostly Type II collagen fibrils), and proteoglycans. The ECM of the articular cartilage contains more than 70% water and over 90% of its dry weight consists of Type II collagen and proteoglycans. Embedded in the ECM are the chondrocytes, the cells of the articular cartilage (Keuttner and Thonar, 1998).

Proteoglycans are polysaccharide chain structures that have an overall negative charge due to their molecular structure. This gives them a high attraction for water. In the ECM of articular cartilage, large numbers of proteoglycans are arranged in aggregates that are tightly bound within a framework of arching collagen fibrils. The collagen fibrils form a tight network that restrains and anchors the water-loaded proteoglycans to keep them in place. This unique structure gives cartilage its properties of tensile strength and resilience. The tensile strength of the collagen resists deformation and maintains the basic structural framework. The proteoglycans, through strong, charged interactions with water, control the flow of solutes and the time-dependent deformation of the cartilage with weight bearing on the joint. This process is similar to that seen when compressing a water-loaded sponge (Keuttner and Thonar, 1998).

The main proteoglycan in cartilage is called aggrecan (the aggregating large proteoglycan), which consists of a protein core to which chondroitin sulfate and keratan sulfate chains are attached. It provides articular cartilage its properties of compressive stiffness. The terminal end of aggrecan can link to hyaluronic acid. The nature and quantity of proteoglycans changes with use and disease (Keuttner and Thonar, 1998).

Chondrocytes are widely disbursed throughout the cartilage, embedded in the ECM. Chondrocytes are the only cells of the articular cartilage. Because the articular cartilage lacks blood vessels, the chondrocytes must receive nutrients and eliminate waste through the process of diffusion. Nutrients and wastes diffuse through the synovial fluid within the joint capsule and through the surrounding blood vessels. Blood vessels are located in the synovial membrane and subchondral bone (Keuttner and Thonar, 1998).

Chondrocytes are metabolically very active; however, they normally do not divide after adolescence. The integrity of the cartilage is dependent on the activity of the chondrocytes. Their function is to regulate both the synthesis and degradation of articular cartilage through the secretion of enzymes. The principal roles of articular cartilage are to:

- reduce friction at the joint
- act as a cushion to absorb the shock associated with joint use
- efficiently transmit weight loads to the underlying bone (Keuttner and Thonar, 1998).

2.5.2 POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS

2.5.2.1 ROLE OF METALLOPROTEINASES (MMP'S)

DJD joints have increased activity of metalloproteinase (MMP) which is an enzyme found in chondrocytes (Schnitzer, 2004). These enzymes have shown to be increased after joint injury; an increase in enzyme activity parallels the increase in release of collagen and proteoglycan fragments. As the different Type II collagen and proteoglycan fragments are released, specific metalloproteinases have been identified that are believed to be central to the degradative process seen in DJD (Mort and Billington, 2001). MMP-13 (collagenase 3) has a high specificity for type II collagen and is now believed to play a central role in cartilage degredation. The predominant proteoglycan in cartilage, aggrecan, is

the substrate for a specific aggrecanase (extracellular protease) but can also be degraded by a number of MMP's (Schnitzer, 2004).

2.5.2.2 ROLE OF CYTOKINES

Once mild synovial inflammation is established, the synovium becomes a source of cytokines, including Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tissue Necrosis Factor-α (TNF-α). These substances diffuse through the synovial fluid and cause further degradation of articular cartilage. IL-1 and TNF-alpha stimulate the chondrocytes to produce more degrading enzymes, and the process continues in a vicious cycle (Keuttner and Thonar, 1998).

2.5.2.3 ROLE OF NITRIC OXIDE

Nitric oxide synthase has also been found in chondrocytes from cartilage affected by DJD and human articular chondrocytes when stimulated by cytokines such as IL-1, release inflammatory mediators including nitric oxide. Nitric oxide may be directly toxic to articular cartilage. One suggested mechanism includes down regulation of IL-1 receptor antagonist resulting in apoptosis of chondrocytes (Creamer and Hochberg, 1997). However further studies need to be conducted to determine the exact role of nitric oxide in cartilage degradation.

2.5.2.4 ROLE OF PROSTAGLANDINS

Studies have shown that IL-1 derived from the osteoarthritic cartilage stimulates the production of prostaglandin E_2 (PGE_2). Once formed, PGE_2 increases the synthesis of stromelysin, a cartilage-degrading protein (MMP). PGE_2 also has important pro-inflammatory properties and contributes to vasodilation and pain in patients with DJD (Keuttner and Thonar, 1998).

2.5.2.5 ROLE OF SUBCHONDRAL BONE

Subchondral bone has long been thought to be thickened in joints involved by DJD. This has been observed on plain radiographs as well as discerned by orthopaedic surgeons at time of total joint replacement (Schnitzer, 2004).

Radin and Rose (1986) as cited by Schnitzer (2004) proposed alterations in underlying subchondral bone stiffness may be an important etiological factor in the subsequent overlying cartilage damage. The analogy used was that of a cushion (cartilage) and a hard chair seat (subchondral bone). If the chair seat is non-uniform in hardness, when it becomes loaded, there will be shear stresses generated across the cushion. Such shear stresses across cartilage could be expected to respond to those abnormal loading forces in a way that ultimately results in breakdown and damage (Schnitzer, 2004).

The first direct experimental data suggesting a link between the subchondral bone and DJD came from a study by Dieppe and colleagues. In this study, 94 patients with DJD of the knees were followed prospectively for 5 years, with longitudinal radiographs to identify joint space narrowing (a measure of loss of joint cartilage) and base line bone scans (technetium-99m scintigraphy). It was observed that there was a close correlation between positive scans and progression of joint space narrowing and/or surgery on the knee. Patients having a negative bone scan had progressions of their knee DJD by radiography or had need for surgery. By contrast, of those knees with positive uptake of radio nuclide, 34% went on to have greater than 2 mm loss of joint space or surgery, and in those knees showing both an early and late (perfusion) phase uptake of isotope, 54% progressed to greater than 2mm joint space loss or knee surgery. Thus, the data strongly support a close relationship between progressive cartilage damage and destruction and underlying bone remodeling activity (Schnitzer, 2004).

2.6 CLINICAL FEATURES

The clinical presentation of the disease depends on the duration, the joints affected, and the severity of the joint involvement. Common joints affected are the weight-bearing joints, which include the spine, hip, knee, and ankle. Other joints affected are the small bone joints of the hands and the feet. Pain is the most common symptom in patients with DJD, associated with the use of the joints (Yasmin *et al.*, 2000).

The pain of DJD may arise from articular and/or peri-articular structures. Articular cartilage is aneural, therefore it is theorized that pain may be due to one or a combination of the following factors:

- Subchondral bone: increased vascularity and activity leads to sclerosis and cysts; increased intraosseous pressure leads to pain
- Joint margin: thickening of the capsule and osteophytes may cause pain
- Capsule and synovium: increased thickness and mild inflammation may cause pain
- Tendons and bursae: periarticular tendinitis and bursitis cause pain, resulting in decreased joint motion, leading to muscle wasting and weakness (Dieppe and Lim, 1998).

Other signs and symptoms include joint margin tenderness, crepitus (cracking or grinding sensation, often audible), features of swellings of soft tissue inflammation, joint effusions, joint locking (giving way) due to loose bodies, joint stiffness, decreased range of motion, local weakness or muscle atrophy, joint instability, and varus or valgus deformities seen with advancing disease (Dieppe and Lim, 1998).

Patients with DJD of the knee typically develop genu varus and more rarely genu valgus. With the increasing deformity, the weightbearing axis shifts toward the

involved compartment of the knee which increases the load on that compartment resulting in pain and aid in the progression of the disease (Oloff, 1994).

It should be emphasized that the risk factors for joint pain and disability in DJD are not the same as risk factors for the failure of articular cartilage and bony changes (Brandt, 1995). Differences in pain severity are influenced by culture, sex and psychosocial factors (Creamer and Hochberg, 1997). Thus, the correlation is poor between the pathological severity of DJD and symptoms. Many individuals with radiographic changes of advanced DJD are asymptomatic, while clinical features of DJD may be present in patients with normal joint radiographs (Brandt, 1995).

The natural history of DJD is highly variable (Creamer and Hochberg, 1997). Disease evolution of knee DJD is slow, usually taking many years. Symptomatic improvement sometimes occurs but spontaneous improvement in radiographic changes are rare. The clinical presentation is often punctuated by symptomatic 'flares', lasting days or weeks, which may be associated with signs of increased inflammation (Dieppe and Lim, 1998). Synovial inflammation DJD may be induced by proteoglycans or cartilage fragments released from the damaged articular surface or by calcium containing crystals, which may result in the release of proinflammatory mediators, e.g. bradykinin and previously mentioned prostaglandins, which sensitizes nociceptors or pain receptors (Bradley and Brandt, 1998). This associated inflammation may be focal with synovial hyperplasia and a dense mononuclear cell infiltrate which is most pronounced where the synovium is adjacent to cartilage (Creamer and Hochberg, 1997). In a few cases the symptoms and signs get worse over a period of few weeks to months. This may be associated with the development of instability or subchondral bone collapse. A sudden instantaneous increase in pain suggests the possibility of medial femoral bone necrosis. Other rare complications of severe disease include tibial fractures, severe instability and gross angulation deformities of the knee (Dieppe and Lim, 1998).

2.7 RADIOGRAPHIC EVIDENCE

According to Yochum and Rowe (1996) there are eight essential signs of degenerative joint disease:

- Asymmetric distribution
- Non-uniform loss of joint space
- Osteophytes
- Subchondral sclerosis
- Subchondral cysts
- Intra-articular loose bodies
- Intra-articular deformity and joint subluxation.

These roentgen signs closely parallel the underlying pathogenic sequence involving the joint components. All signs will not necessarily be present in every case of degenerative joint disease (Yochum and Rowe, 1996).

A study by Lanyon *et al.* (1998), evaluated radiographic features of DJD to determine which is more closely associated with knee pain and hence might be used as a radiographic definition of DJD in the community. They concluded that osteophytes are the radiographic feature that associates best with knee pain. Their results showed that joint space loss is not a feature of asymptomatic aging. This finding that joint space does not necessarily decrease with age among asymptomatic subjects supports the concept that DJD is a part of aging or "wear and tear" (Lanyon *et al.*, 1998).

In an earlier study, Ledingham *et al.* (1995) evaluated prognostic significance of patient symptoms and radiographic features of DJD knees of 350 patients over a two year period. They found that the development of, or increase in, bone attrition and joint space narrowing associated with worsening of symptoms and function occurred with increased frequency in knees with effusion, clinical warmth and calcium pyrophosphate crystals in synovial fluid ($p<0.05$) (Ledingham *et al.*, 1995).

Radiographs are relatively insensitive for detection of early DJD and minor progression of cartilage and bone change. It serves as a static assessment of DJD which provides an anatomical record of prior DJD changes. Scintigraphy and magnetic resonance imaging (MRI) are more informative of current dynamic, physiological change (Jewell *et al.*, 1998). Despite the advantages of high resolution and this ability to produce images in any desired plane, MRI is costly and relatively unavailable (Cooper and Dennison, 1998). Plain radiographs which are readily available and relatively inexpensive (Dieppe *et al.*, 1998) remains the dominant imaging modality in the diagnosis and assessment of OA (Jewell *et al.*, 1998).

2.8 THE HARPAGO AND CELERY SEED CREAM

The Harpago and celery seed cream is a topical agent manufactured by the House of Health (South Africa). It contains two active ingredients which are proposed to control pain and inflammation. The two components are extracts of *Harpagophytum procumbens* (Devil's Claw) and extracts of *Apium graveolens* (Celery seed). Each 25 grams of the cream contains Harpago concentrated extract and 10% Celery Seed extract. The biochemical analysis of the Harpago and celery seed cream as provided by the manufacturers indicated in Appendix K.

Currently there are no other topical agents similar to the Harpago and celery seed cream and none which contain both components. The researcher was informed by the manufacturers of the product that there were no existing clinical trials investigating its efficacy in any particular condition or the creams rate of uptake and depth of penetration.

2.8.1 PROPOSED MECHANISM OF ACTION

There are two pathways involved in initiating the inflammatory process viz. the lipoxygenase pathway and the cyclo-oxygenase pathway. Arachidonic acid, a 20-carbon polyunsaturated fatty acid is a component of cell membrane phospholipids and is released due to the activation of the phospholipases by mechanical, chemical, physical stimuli, or by inflammatory mediators such as C5a. Arachidonic acid metabolism proceeds along one of the above mentioned inflammatory pathways, named for the enzymes that initiate the reactions. The activation of the lipoxygenase enzymes results in prostaglandin synthesis while the activation of the cyclo-oxygenase enzymes results in leukotriene synthesis, both promoting inflammation (Mitchell and Cotran, 1999).

The *Harpagophytum procumbens* extracts contain a variety of compounds, mainly iridoid glycosides which are a group of terpenoid plant compounds or phytochemicals that are considered pharmacologically active. The fraction of iridoid glycosides consists of harpagoside, procumbide, harpagid, and 8-para-coumaroyl-harpagid (Wegener, 2000). Harpagoside is the primary iridoid glycoside which is proposed to inhibit leukotriene biosynthesis (Eich *et al.*, 1998).

In an uncontrolled study conducted by Wegener and Lupke (2003), 75 patients with arthrosis of the hip and knee were treated with aqueous extracts of the *Harpagophytum procumbens.* Subjects received daily dosage of 2 tablets thrice daily containing a total dosage 50 mg of harpagoside over 12 weeks. Subjects were assessed after 6-week intervals using the WOMAC osteoarthritis index and Visual Analogue Scale (VAS). Results revealed improvements in each of the WOMAC subscales: 23.8% for the pain subscale, 22.2% for the stiffness subscale and 23.1% for the physical function subscale. The WOMAC total score was reduced by 22.9%. VAS pain scores were decreased by 25.8% for actual pain, 25.2% for average pain, 22.6% for worst pain and 24.5% for the total pain

score. Physicians noted an improvement in physical findings: 45.5% for pain on palpation, 35% for limitation of mobility and 24.5% for joint crepitus.

The active biochemical components from *Apium graveolens* (celery seed) extracts display prostaglandin H endoperoxide synthase-I (COX-I) and prostaglandin H endoperoxide synthase-II (COX-II) inhibitory activities (Momin and Nair, 2000), thus inhibiting pain and inflammation. The active components in celery seed extracts are natural occurring phthalides or phytochemicals, in particular 3-n-butylphthalide (3nB) (Murray, 2003).

In a study conducted by Sounderajan and colleagues as cited by Murray (2003), a celery extract standardized to contain 85% of celery phthalides had been evaluated in the treatment of degenerative joint disease, osteoparosis and gout. During the active phase of the 12-week pilot study, the 15 subjects suffering from either degenerative joint disease, osteoparosis or gout received oral doses of 34 mg of a proprietary celery extract standardized to contain 85% celery seed phthalides twice daily. Subjects experienced significant pain relief after 3 weeks of use with the average reduction in pain scores of 68% and some subjects experiencing complete 100% relief from pain. A larger study was conducted using 70 patients. Test subjects received 75 mg of the celery seed extract twice daily for three weeks. At this higher dosage, statistically and clinically significant reductions were noted in pain scores, mobility, and quality of life (Murray, 2003).

It must be noted that the above clinical trials used oral agents which were prepared to contain the active components of, the *Harpagophytum procumbens* and *Apium graveolens* individually and its efficacy as a combined topical agent is unknown.

2.9 CURRENT MANAGEMENT OF DJD

The primary goal of treatment of DJD is to control pain and to maintain the normal function of the joints to improve the quality of life of the patient (Yasmin *et al.*, 2000).

Pharmacological treatments, which are used for the management of DJD of the knee fall primarily into the "symptom modifying" category of DJD drugs. Pain remains the major indication for DJD therapy and relief of pain the major aim of treatment (Brady *et al.,* 1997). Traditionally, pharmacological treatment for DJD has been based on the use of nonsteroidal anti-inflammatory drugs (NSAID's) since it was believed that inflammation was the cause of pain in DJD. However, studies have shown that patients with knee DJD have pain without synovitis, and patients with knee pain and synovitis respond to pharmacological therapy similarly to those without synovitis (Lane and Thompson, 1997).

NSAID's can give rise to acute renal insufficiency, interstitial nephritis with proteinuria, prolonged bleeding time (due to platelet inhibition), tinnitis, headaches, confusion, depression, rashes, hypersensitivity reactions and hepatic toxicity. The major side effect, however, and most common cause of morbidity due to NSAID's is gastrointestinal toxicity (Ratiner and Lane, 2000). Recently, concerns have been expressed about the possibility that some NSAID's (indomethacin, aspirin and the more potent prostaglandin inhibitors) may accelerate the process of cartilage destruction in DJD (Rainsford, 1999). Huskisson *et al.* (1995) performed a study to compare the rate of radiographic progression in knee DJD between indomethacin with placebo and tiaprofenac acid with placebo. They concluded that indomethacin increased the rate of radiological deterioration of joint space in patients with DJD of the knee.

In patients with DJD of the knee who do not respond to oral analgesics or who do not wish to take systemic therapy, Hochberg *et al.* (1995) are of the opinion that

the use of topical agents is appropriate. However, in the study conducted by Tugwell *et al.* (2004), 622 patients with knee DJD were treated with either topical and oral diclofenac over twelve weeks, and results showed that there was no significant difference in pain scores but the physical function scores (WOMAC Index) were significantly more improved with oral diclofenac (Bookman *et al.*, 2004). According to a meta-analysis of clinical trials by Mason *et al.* (2004), three trials compared topical NSAID's with oral NSAID's in patients with DJD of the knee and finger joints, there was no statistically significant difference between routes of administration. One clinical trial by compared piroxicam 0.5% gel with oral ibuprofen 1200 mg daily, another compared diclofenac 1% gel with oral ibuprofen 1200 mg daily and the third compared eltenac 1% gel with oral diclofenac 100 mg daily. In these trials, with 764 patients, 37% had a successful outcome both with topical NSAID's and oral NSAID's. There was no statistically significant difference (relative risk 1.1; 95% CI 0.9 to 1.3) (Mason *et al.*, 2004). Patients who are unwilling or unable to take oral NSAID's can utilize topical therapies as an effective adjunct to analgesic agent or as a form of monotherapy (Hochberg-NIH Conference 2000).

Surgical management of DJD is considered only after failure of non-surgical treatments. Four categories of non-biological procedures are considered surgical management: osteotomy, arthroscopy, arthrodesis and arthroplasty (Hochberg-NIH Conference, 2000).

Osteotomies are performed in patients with early DJD and may relieve symptoms and slow the rate of progression. Arthroscopic debridement and lavage can also successfully alleviate symptoms, particularly in the case of degenerative meniscal tears in the presence of mechanical symptoms. However, where there is substantial joint space narrowing, arthroscopic surgery has limited benefit. Arthrodesis or joint fusion, successfully alleviates pain and is commonly performed in the spine and in the small joints of the carpus, hand and foot (Hochberg- NIH Conference, 2000). However, anterior arthrodesis has also been

shown to predispose to adjacent-level degeneration. The immobilization of one motion segment may cause increased stress at the adjacent level, most frequently at the level superior to the fusion. Spondylosis or disc herniation at the level above a previous fusion may cause new radiculopathy or myelopathy (Eichholz and Ryken, 2003). Arthrodesis of the major proximal joints of the upper and lower extremities is not well tolerated because of major functional deficits associated with a loss function. Total joint arthroplasty represents the most significant advancement in the treatment of DJD in the past century. It is the mainstay of surgical treatment for knee DJD. Total joint replacement has limited durability in persons with life expectancies exceeding 20 years and those who wish to participate in high demand activities. the most common reasons for failure of joint replacement surgery are aseptic loosening and osteolysis, processes that are time and activity dependant (Hochberg-NIH Conference, 2000). Although there are a few randomized controlled clinical studies of knee replacements, there is a large amount of observational evidence that knee replacements reduce pain and improve function. The failure rate is around 1% over 10 years. Around 12-20% of people continue with at least moderate knee pain following surgery (Underwood, 2005).

There are a number of non-pharmacological therapies available for knee DJD. Indeed, many non-pharmacological therapies are fundamental to the treatment of any chronic disease (Lane and Thompson, 1997). Adjunct non-pharmacological treatment of DJD includes:

- Patient self-management programs conducted at Rheumatology Clinics at state hospitals and by independent arthritis associations
- Weight loss if overweight (Body Mass Index-BMI > 25.0)
- Physical therapy which includes, range of motion exercises, muscle strengthening exercises, and use of assistive devises of ambulation
- Occupational therapy, including occupational therapy, including joint protection and energy conservation, use of assistive devices for activities of daily living (canes, walkers, braces)

- Aerobic aquatic exercise programs and health professional and social support (Yasmin *et al.*, 2000).

Exercise and physical therapy are considered an important part of rehabilitation programs for patients with DJD as this helps patients to regain joint mobility and function (Deyle *et al.,* 2000). A randomized controlled clinical trial conducted by Fransen *et al.* (2001), evaluating the efficacy of physical therapy and exercise on 126 patients, confirmed the effectiveness of physical therapy for patients with knee DJD seeking treatment in terms of self-reported pain, physical function and health related quality of life. Improvements revealed by self-reported questionnaires ($p<0.01$) were significantly associated with improvements in objective measures of physical performance regarding knee extensor strength ($p=0.01$) and fast walking speed ($p<0.01$), and treatment effectiveness was still apparent 2 months after receiving treatment.

2.10 CONCLUSION

The review of the literature reveals that DJD of the knee is a prominent condition with numerous causative factors and mechanisms involved in its pathogenesis. Although non-fatal, DJD is still responsible for much pain, disability, and emotional suffering. DJD of the knee requires an integrated treatment regime to assist with symptom relief particularly in the early course of the disease. Due to the fact there are no specific curative mechanisms or agents for this disease, the goal of all therapeutic approaches is aimed at slowing down the arthritic process, alleviating the symptoms experienced and improving the patients' quality of life.

The Harpago and celery seed cream is a natural non-invasive therapy. It uses a combination of extracts which are proposed to assist pain relief and secondary inflammation associated with DJD. There are no known side effects and there is no risk of overdosing.

This study will determine the efficacy of the Harpago and celery seed cream in the management of mild to moderate degenerative joint disease of the knee.

CHAPTER 3

3.0 MATERIALS AND METHOD

3.1 INTRODUCTION

This chapter deals with the details of the research study undertaken. This includes a detailed description of the design, primary and secondary data, the subjects and interventions used. Statistical procedures for the assessment of the data are discussed as well.

3.2 RESEARCH DESIGN

The research design was a double-blinded, placebo-controlled, randomized clinical trial where the Harpago and celery seed cream was evaluated for its efficacy in the treatment of subjects with mild to moderate degenerative joint disease (DJD) of the knee.

3.3 STUDY DESIGN PROTOCOL

3.3.1 SUBJECT RECRUITMENT

Subjects were obtained from the greater Durban functional region using advertisements placed in public places (e.g. gymnasia, local community notice boards, senior citizen associations and libraries), pamphlet distribution and newspaper advertisements, inviting free participation in a clinical trial for persons with degenerative joint disease of the knee. The advertisements called on patients having knee pain for six months or more and those who had been previously diagnosed with degenerative joint disease of the knee. There were no restrictions on ethnicity, cultural or socioeconomic background.

Upon reply, each subject was telephonically interviewed so as to explain the conditions of the study and as an initial screening process, with questions pertaining to the history and progression of their complaint, to eliminate those obviously falling outside the range of the study. The following questions were asked:

- Are you between the ages of 35 to 68?
- Have you been diagnosed with osteoarthritis or currently have knee pain?
- How long have you been suffering from this?
- Do you have any existing medical conditions?
- Are you currently on any medication?
- Have you had any knee surgery recently in the last 5 years?
- Are you pregnant or breast -feeding?
- Have you had any x-rays taken recently?

From those selected telephonically, the initial consultation was scheduled for the prospective participant at the Durban Institute of Technology's Chiropractic Day Clinic.

3.3.2 THE INITIAL CONSULTATION

At the initial consultation, the participants underwent a case history (Appendix A), a relevant physical examination (Appendix B), and a knee orthopaedic examination (Appendix C). Appointments for knee radiographs were then scheduled for all participants to confirm radiological diagnosis of mild to moderate DJD of the knee.

3.3.2.1 INCLUSION CRITERIA

1) Subjects were between the ages of 35 to 70 years. The prevalence of people affected by DJD of the knee is predominantly over the age of 35.

Those over the age of 70 were excluded as the probability of late DJD changes noted in this age group is high.

2) Only subjects diagnosed by the researcher as a having mild to moderate DJD (as discussed in Chapter 2) were included in the study. The diagnosis was confirmed by consulting a clinician and discussing the findings from the case history, clinical examination and radiological findings of each subject. A clinical diagnosis of DJD was made using the following criteria according to Dambo and Griffiths (1995).
    - Slowly developing knee joint pain in one or both knees
    - Decreased range of motion
    - Pain in the involved knee that is aggravated by activity and relieved by rest
    - Morning stiffness upon rising or stiffness after disuse
    - Joint crepitus
    - Tenderness along joint margins
3) The evidence of radiographic DJD according to Yochum and Rowe (1996), should include:
    - Non-uniform loss of joint space
    - Subchondral bony sclerosis
    - Osteophyte formation
    - Increase in soft tissue swelling

For this study any three of the above criteria were accepted as radiographic evidence of DJD.

3.3.2.2 EXCLUSION CRITERIA

1) Subjects on any form of medication specifically for the condition or those receiving any other form of treatment were excluded from the study.
2) Pregnant or lactating females.

3) Subjects were excluded if they presented with, or if they had showed any indication that they may have had any of the following:
    - Grade 3 ligamentous instability of the knee
    - Neoplastic disease
    - Infective arthritides and inflammatory arthritides
    - Haematological diseases
    - Metabolic bone diseases
    - Unhealed fractures
    - Broken or fragile skin, dermatoses or infection of the application site
    - Late radiographic signs of DJD: arthritic fusion, joint destruction and subluxation
    - Participants refusing to sign the informed consent form

3.3.2.3 INFORMED CONSENT

Once subjects met the inclusion criteria, they were given a patient information letter (Appendix D) regarding the research process and their participation. They were then, asked to complete and sign an informed consent form (Appendix E).

3.3.2.4 INITIAL ASSESSMENTS

Subjective data using the Numerical Pain Rating Scale-101 (NRS101) (Appendix F), and the Patient Specific Functional Scale (PSFS) (Appendix G) while objective data using algometer and inclinometer readings were obtained prior to the application of the intervention and recorded on data sheets (Appendices H and I).

3.3.2.5 INTERVENTION APPLICATION INSTRUCTIONS

The subjects were instructed to self-treat at home with their randomly selected intervention, either the Harpago and celery seed cream or placebo aqueous cream. No specific application or dosage instructions were given by the manufacturers. It was decided by the researcher in consultation with clinicians at the Chiropractic Day Clinic on a standard dose and application time. Subjects were instructed to apply and massage (3 minutes) a small amount of the product (the size of a 20 cent piece/1.5 cm diameter on their palm) to only the affected area around the knee twice daily for a period of two weeks. Strict instructions to self-administer the cream for the above given time for each application were given to all subjects to maintain standardization. They were also given a time sheet (Appendix J) to complete everyday noting the date and time of the two applications to record consistency. Each subject was also instructed to begin the day after the initial consultation, with the initial application for the day being between 6 to 10 am and the second application for the day being between 6 to 10 pm to maintain standardization among subjects.

3.3.2.6 BLINDING PROCESS AND GROUP ALLOCATION

The placebo used was an aqueous cream contained in the same packaging as the original Harpago and celery seed cream. There was no difference in appearance between the active cream and the placebo cream. The placebo and the active creams were placed in separate boxes (Box A- Active creams and Box B-Placebo creams).

Convenience sampling was utilized in this study. After recording the initial readings with regard to pain and range of motion on the first consult, each subject was then sent to reception. At reception, the subject was asked to pick a piece of paper containing either the letter A or B out of a hat and collect the appropriate cream (A-active or B-placebo) from designated reception staff at the

Durban Institute of Technology's Chiropractic Day Clinic. The name and the corresponding letter chosen were recorded on two separate lists by the designated reception staff for future reference for the researcher. The reception staff were instructed not to reveal any information regarding the subject's group allocation or intervention. The corresponding cream was then given to the subject. The researcher was unaware of which cream was given to any particular subject. The second consultation was scheduled for a week later.

3.3.3 THE SECOND CONSULTATION

At the second consultation after the first week of application, the subjective and objective assessments were obtained again using the assessment tools utilized at the first consultation. The time sheet was also reviewed to ascertain consistency of applications. The third consultation was then scheduled for a week later.

3.3.4 THE THIRD CONSULTATION

Assessments were recorded as mentioned in the second consultation. Those receiving the placebo were informed that they were entitled to two free treatments for their condition at the Durban Institute of Technology's Chiropractic Day Clinic.

3.4 ETHICS

All ethical procedures were implemented according to the Durban Institute of Technology's Faculty of Health Ethics Committee guidelines (Appendix L). All subject information was treated as confidential and kept at the Durban Institute of Technology's Chiropractic Day Clinic. Data collected will be shredded after a period of five years. Subjects were informed that they were free to withdraw from the study at any time.

3.5 THE DATA

This consisted of primary and secondary data.

3.5.1 THE PRIMARY DATA

This consisted of:

- The demographic data obtained from the case history.
- Knee ranges of motion measured with the Digital Inclinometer.
- Pain threshold measured with an algometer.
- Subjects' perception of their worst and least levels of pain intensity using the Numerical Pain Rating Scale.
- Subjects' perception of their disability using the Patient-Specific Functional Scale (P.S.F.S).

3.5.2 THE SECONDARY DATA

This consisted of documents and relevant literature obtained from various sources containing applicable information relating to this study. Information was acquired from journals, books and medical search engines on the Internet (Medline, Mantis and Medscape).

3.6 SUBJECTIVE MEASUREMENTS

3.6.1 THE NUMERICAL PAIN RATING SCALE-101 (NRS-101)

The NRS-101 (Appendix F) is a questionnaire used to assess the subjects' perceived level of pain intensity.

The subject was presented with two lines, each marked with "0" at one end and "100" at the other. The subject was then informed that "0" represented "no pain" and "100" represented "pain as bad as it could be". On the first line, the subject was asked to identify the number which best represented the level of pain they were experiencing when the pain was at its worst. On the second line, the subject was asked to identify the number which best represented the level of pain they were experiencing when the pain was at its least. The average between these two figures was then taken as the percentage intensity of pain they were experiencing.

Jenson *et al.* (1986) established N.R.S's validity and reliability when providing subjective information about pain levels. This scale is simple to administer and score, and can be administered either in written or verbal form. The authors also believe that this is the most practical and superior index.

3.6.2 THE PATIENT SPECIFIC FUNCTIONAL SCALE (P.S.F.S)

The P.S.F.S. (Appendix G) was developed by Stratford and colleagues to provide a method for eliciting, measuring and recording descriptions of patients' disabilities (Chatman *et al.*, 1997).

Subjects were asked to identify three important activities that they were having difficulty with or unable to perform. In addition to specifying the activities, subjects were asked to rate their current level of difficulty associated with each activity.
The scale anchors are 0 ("unable to perform the activity") to 10 ("able to perform activity at same level as before injury or problem"). At each visit, the subject was reminded of the activities that were listed at the first consultation and were then re-evaluated.

The P.S.F.S is a time efficient and appropriate tool when the goals of the assessment of disability with a focus on function rather than impairment. Test-

retest reliability and sensitivity to change were excellent (intra-class correlation coefficient [type 2.1] R=0.84 and Pearson's R=0.78, respectively). Validity was also confirmed (Chatman *et al.*, 1997).

3.7 OBJECTIVE MEASUREMENTS

3.7.1 THE DIGITAL INCLINOMETER

The Digital Inclinometer measuring knee range of motion in flexion and in extension was used. Subjects were asked to lie prone on an examination bed with their feet over the distal end of the bed to keep the knee joint in the neutral non- weight bearing position. A strap was placed around the calf of the involved knee to which the digital inclinometer was placed perpendicular to the bed in the sagittal plane. The inclinometer was then recalibrated to "0". Extension was then measured by asking the subjects to drop the knee over the lateral aspect of the bed and the reading was noted for extension. The subjects were then asked to place their knee in the neutral position and again, the inclinometer was recalibrated to "0". Flexion was then measured by asking the subjects to bend their knee as far was possible and again the reading was noted for flexion. (Appendix H)

The instrument used in this study was the Saunders Digital Inclinometer. (The Saunders Group Inc. 4250 Narex Drive, Chask, Minnesota. 5531-3047, USA)

3.7.2 THE ALGOMETER

The algometer readings were used to quantify any changes in the subjects pressure pain threshold.

Fischer (1986) stated that pain can be quantified by pressure threshold measurement, and that changes in the patients pressure threshold under

standard clinical conditions can be regarded as reliable data. The higher the reading, the less tenderness is present. Improvement is shown by a higher threshold.

The procedure for assessing the pain threshold was as follows:

- The algometer dial was reset to zero
- The disc was placed over the "most painful" area perpendicular to the skin and pressure was applied at the rate of one kilogram per second
- The subject was instructed through vocal feedback, when the sensation changed from pressure to pain or discomfort, at which point the pressure was released and the reading was recorded on Appendix I
- Thereafter, the spot which was described as "most painful" was marked with Henna dye to ensure consistent placement of the algometer disc for future consultations

The instrument used in this study was the Wagner Force Dial. (Wagner Instruments: P.O. Box 1217, Greenwich CT 06836, USA)

3.8 STATISTICAL ANALYSIS

The SPSS (version 11.5) statistical package (as supplied SPSS Inc. Chicago, Illinois, USA) was used for data entry and analysis. The statistical evaluation was aimed at measuring whether any significant changes occurred from the initial consultation prior to treatment, to both the second and the third consultation in both groups.

Demographics were compared between treatment groups using Pearson's chi square tests or Fisher's exact tests where appropriate in the case of categorical variables. The t-tests for quantitative normally distributed variables were used to

analyze any significant changes among them between the two groups. Repeated measures ANOVA was used to examine the treatment effect versus the placebo effect for all quantitative outcomes. Visual summaries of analytic findings using profile plots were generated to graphically compare trends over time between the two groups. The data was analyzed at a 95% level of significance i.e. $p<0.05$ was considered as statistically significant.

CHAPTER 4

4.0 THE RESULTS

4.1 INTRODUCTION

This chapter discusses the statistical analysis of the data collected from the study using the methodology outlined in chapter three. Also presented is the interpretation of the results with relevant tables and graphs.

Groups: n=60

- Group A - Active treatment group (Harpago and celery seed cream)
- Group B - Placebo treatment group (Aqueous cream)

4.2 THE ANALYZED DATA

4.2.1 HYPOTHESES TESTING

The null hypotheses (H_o) stated there was no difference between the two treatment groups being compared in terms of subjective and objective clinical findings.

The alternate hypotheses (H_a) stated there was a difference between the two treatment groups being compared in terms of subjective and objective clinical findings. The data was analyzed at $\alpha=0.05$ level of significance.

Decision Rule:

If $p \leq \alpha$, reject the null hypotheses (H_o) and accept the alternate hypotheses (H_a).

If $p > \alpha$, accept the null hypotheses (H_o) and reject the alternate hypotheses (H_a).

Abbreviations used in statistical analysis:

Time – represents the changes in both groups over time.

Time*group – indicates the treatment effect, i.e. if there were any significant interaction between both groups in terms of efficacy of the treatment over time.

Group – indicates the change in both groups regardless of time.

KEY : GRAPHIC ANALYSIS

TIME = Consultation

4.3 STATISTICAL ANALYSIS

4.3.1 DEMOGRAPHIC DATA

TABLE 4.1: GENDER DISTRIBUTION WITHIN THE SAMPLE OF SIXTY

			GROUP		Total
			Active	Placebo	
SEX	Male	Count	4	5	9
		% within GROUP	13.3%	16.7%	15.0%
	Female	Count	26	25	51
		% within GROUP	86.7%	83.3%	85.0%
Total		Count	30	30	60
		% within GROUP	100.0%	100.0%	100.0%

Fisher's exact p=1.000

The sample consisted of 60 participants randomized into two equal groups. Table 4.1 shows that overall there was a higher proportion of females in the sample (85%) relative to males (15%), however, the distribution of sexes between the groups was the same (p=1.000).

TABLE 4.2: COMPARISON OF MEAN AGE BY GROUP WITHIN THE SAMPLE OF SIXTY

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	p value
AGE	**active**	30	54.67	8.719	1.592	0.459
	placebo	30	53.03	8.261	1.508	

Age was not significantly different between the groups (p=0.459). Table 4.2 shows that the mean age of the active group was 54.67 and of the placebo group was 53.03 years. Thus the two groups were comparable in terms of confounders at baseline.

TABLE 4.3: ETHNIC DISTRIBUTION WITHIN THE SAMPLE OF SIXTY

			GROUP		Total
			active	**placebo**	
RACE	Indian	Count	27	26	53
		% within GROUP	90.0%	86.7%	88.3%
	Black	Count	1	2	3
		% within GROUP	3.3%	6.7%	5.0%
	White	Count	2	2	4
		% within GROUP	6.7%	6.7%	6.7%
Total		Count	30	30	60
		% within GROUP	100.0%	100.0%	100.0%

Pearson's chi square =0.352, p=0.839

Table 4.3 shows that there was no significant difference between the racial distributions of the two groups (p=0.839). Both groups consisted of mainly Indian participants, with minor proportions of Blacks and Whites.

TABLE 4.4: AFFECTED KNEE WITHIN THE GROUP IN THE SAMPLE OF SIXTY

			GROUP		TOTAL
			active	placebo	
KNEE	Right	Count	7	12	19
		% within GROUP	23.3%	40.0%	31.7%
	Left	Count	14	15	29
		% within GROUP	46.7%	50.0%	48.3%
	Both	Count	9	3	12
		% within GROUP	30.0%	10.0%	20.0%
TOTAL		Count	30	30	60
		% within GROUP	100.0%	100.0%	100.0%

Pearson's chi square 4.350, p=0.114

Table 4.4 shows that the affected knee was not significantly different between the groups (p=0.114). The left knee was the predominantly affected knee in both groups.

4.3.2 BASELINE COMPARISON BETWEEN GROUPS

TABLE 4.5: COMPARISON OF MEAN BASELINE OUTCOME VALUES BETWEEN THE GROUPS

	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P value
NRS	active	30	50.95	15.894	2.902	0.643
	placebo	30	49.02	16.278	2.972	
PSFS ACTIVITY 1	active	30	4.00	1.983	.362	0.507
	placebo	30	4.37	2.266	.414	
PSFS ACTIVITY 2	active	30	4.10	2.107	.385	0.190
	placebo	30	3.43	1.775	.324	
PSFS ACTIVITY 3	active	30	4.20	1.864	.340	0.403
	placebo	30	3.73	2.392	.437	
ALGOMETER	active	30	4.583	1.5636	.2855	0.071
	placebo	30	5.430	1.9787	.3613	
FLEXION	active	30	88.97	17.804	3.251	0.919
	placebo	30	88.53	15.058	2.749	
EXTENSION	active	30	5.90	2.339	.427	0.958
	placebo	30	5.93	2.545	.465	

Table 4.5 shows that there were no significant baseline differences between the groups for any of the outcomes measured. Only algometer baseline measurements approached statistical significance (p=0.071) with the placebo having marginally higher baseline values than the active group.

4.4 INTRA-GROUP COMPARISONS

TABLE 4.6: INTRA GROUP ANALYSIS FOR NRS SCORES IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultations 2	36.858	<0.001
	Consultation 2 vs. consultation 3	9.290	0.005
	Consultation 1 vs. consultation 3	48.102	<0.001

Table 4.6 shows that within the active group, there was a highly significant decrease in NRS scores between consultation 1 and 2, and also between consultation 1 and 3. This is also shown in Figure 1.

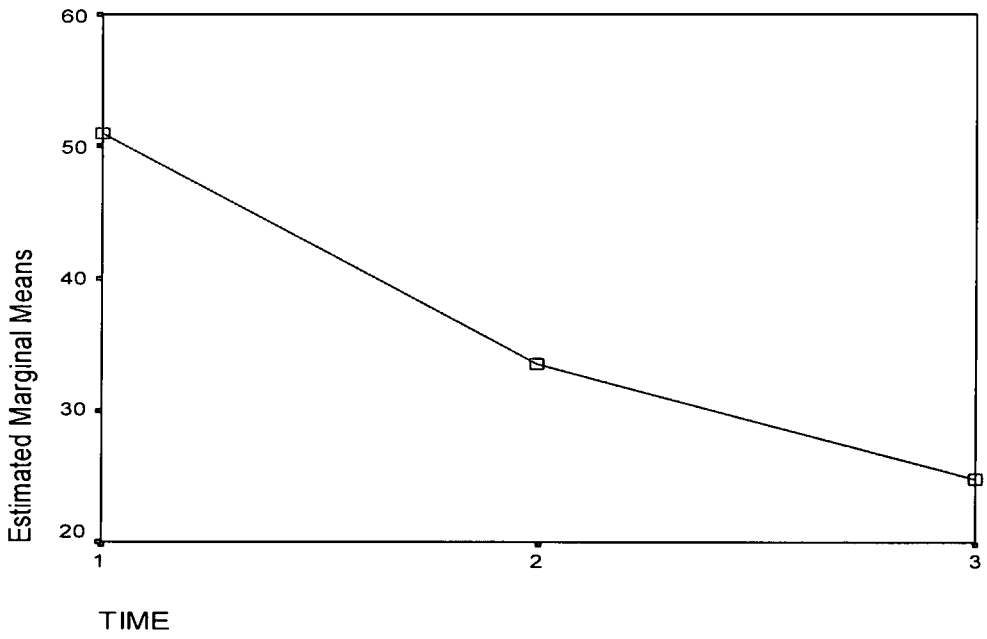

Figure 1: Profile plot of mean NRS scores in the active group

TABLE 4.7: INTRA GROUP ANALYSIS FOR NRS SCORES IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 2 vs. Consultation 1	23.496	<0.001
	Consultation 2 vs. Consultation 3	0.006	0.939
	Consultation 3 vs. Consultation 1	21.919	<0.001

The placebo group also showed a highly significant decrease in NRS scores between consultation 1 and 2, and also between consultation 1 and 3, but there was no significant change between consultation 2 and 3. This is also shown in Figure 2.

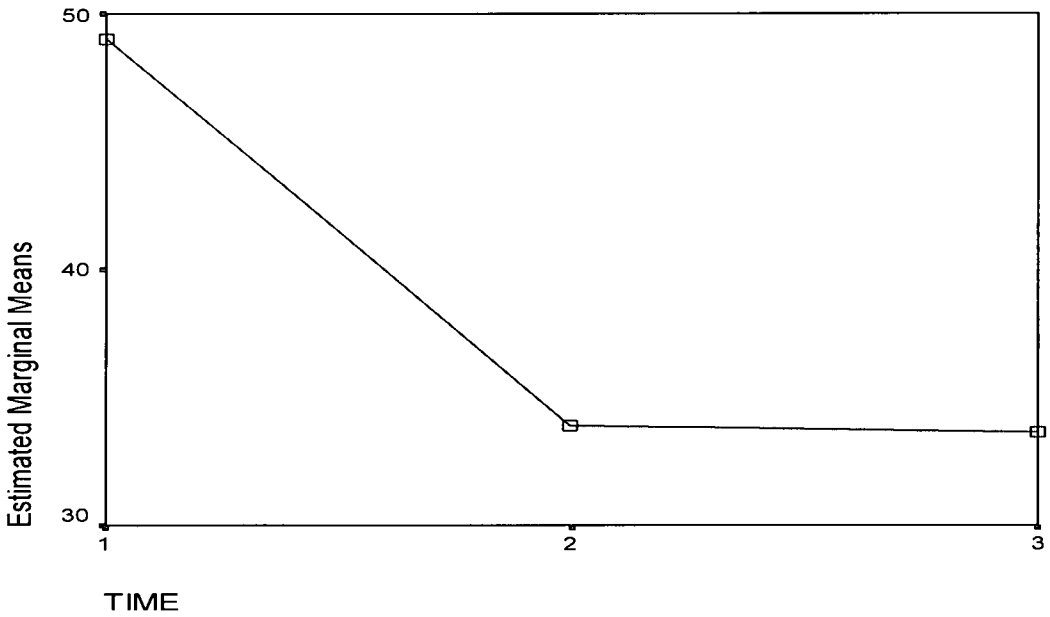

Figure 2: Profile plot of mean NRS scores in the placebo group

TABLE 4.8: INTRA GROUP ANALYSIS FOR PSFS SCORES FOR ACTIVITY IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 2 vs. Consultation 1	25.108	<0.001
	Consultation 2 vs. consultation 3	16.749	<0.001
	Consultation 3 vs. Consultation 1	66.416	<0.001

The active group showed highly significant increases in mean PSFS scores for activity 1 between all the time points as shown in Figure 3.

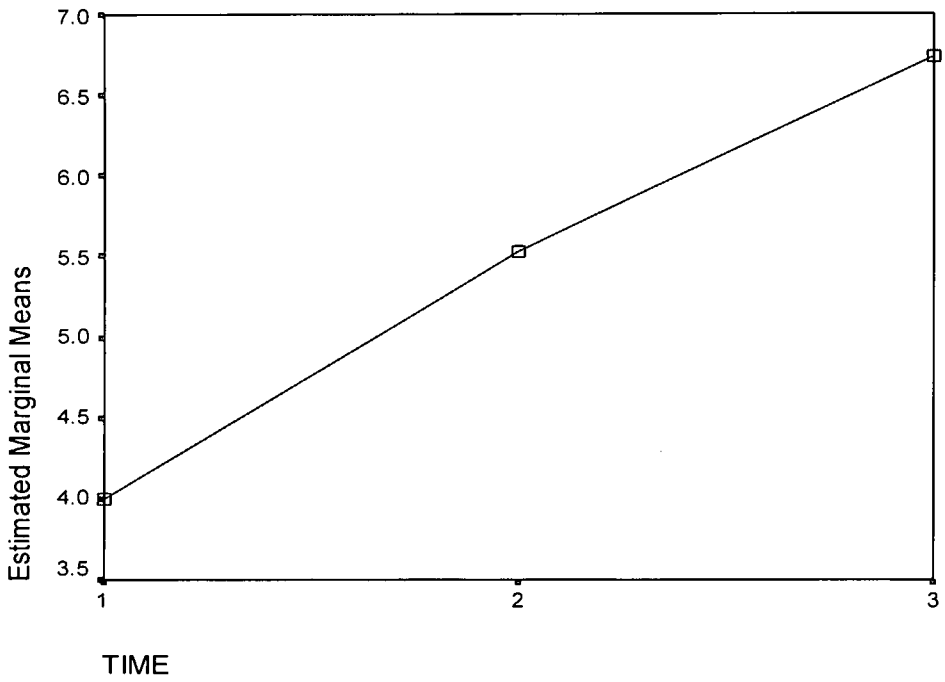

Figure 3: Profile plot of mean PSFS scores- Activity 1 in the active group

TABLE 4.9: INTRA GROUP ANALYSIS FOR PSFS SCORES- ACTIVITY 1 IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	12.942	0.001
	Consultation 2 vs. consultation 3	5.659	0.024
	Consultation 1 vs. consultation 3	18.179	<0.001

The placebo group showed highly significant increases in mean PSFS scores for Activity 1 between all the time points. See Table 4.9 and Figure 4.

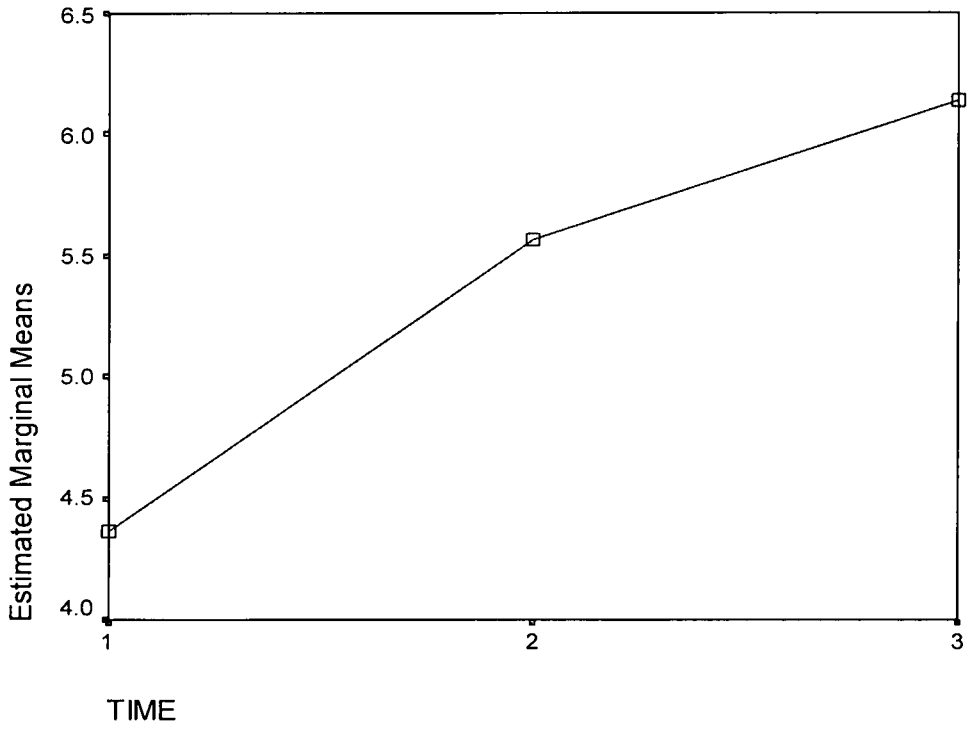

Figure 4: Profile plot of mean PSFS scores- Activity 1 in the placebo group

TABLE 4.10: INTRA GROUP ANALYSIS FOR PSFS SCORES- ACTIVITY 2 IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 2 vs. Consultation 1	17.865	<0.001
	Consultation 2 vs. Consultation 3	28.684	<0.001
	Consultation 3 vs. consultation 1	42.758	<0.001

Activity 2 showed a highly significant increase over all time points, as shown in Table 4.10. A linear increase is shown in Figure 5.

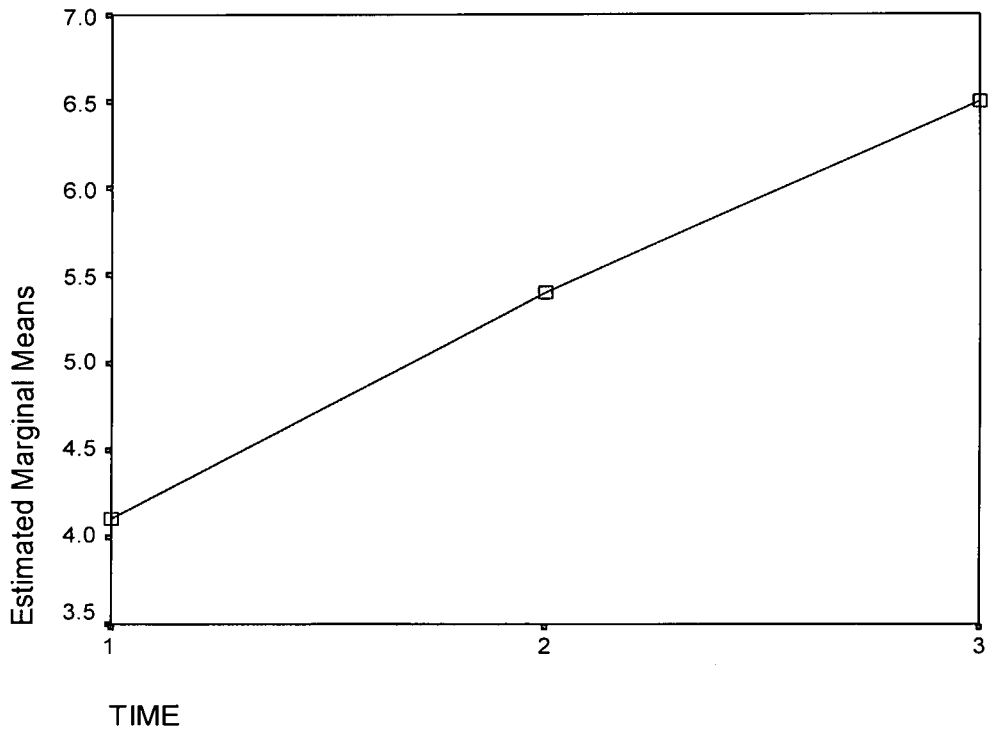

Figure 5: Profile plot of mean PSFS scores- Activity 2 in the active group

TABLE 4.11: INTRA GROUP ANALYSIS OF PSFS SCORES- ACTIVITY 2 IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 2 vs. consultation 1	12.752	0.001
	Consultation 2 vs. consultation 3	2.387	0.133
	Consultation 3 vs. consultation 1	18.209	<0.001

Mean scores for activity 2 also changed significantly between consultation 1 and consultation 2 in the placebo group, however between consultation 2 and 3 there was no significant change as shown in Figure 6.

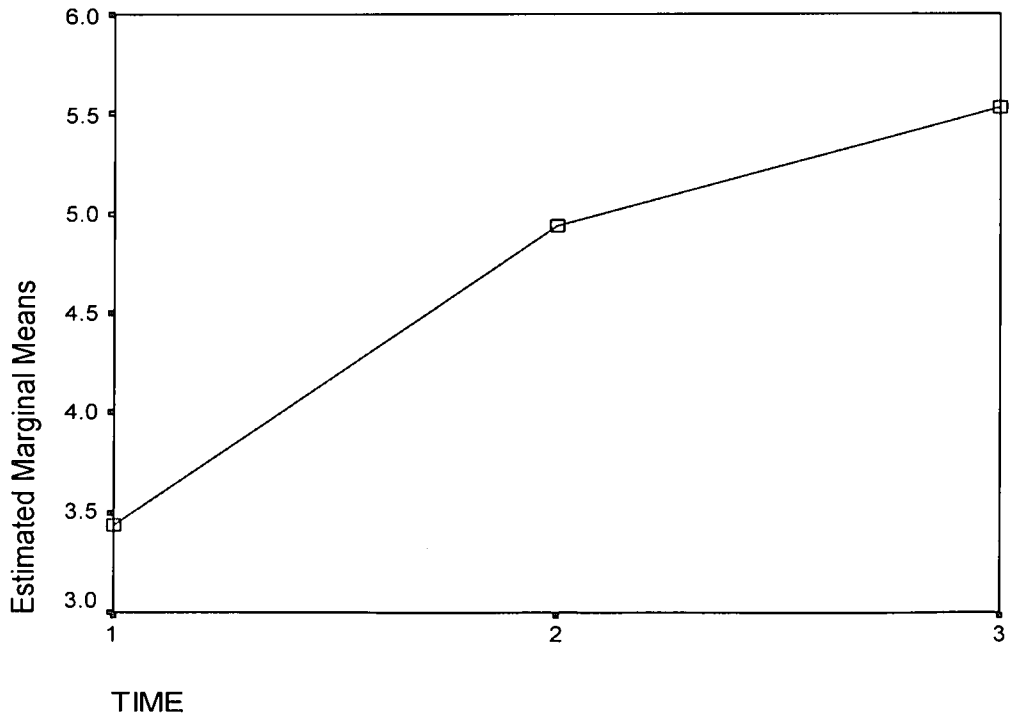

Figure 6: Profile plot of mean PSFS scores- Activity 2 in the placebo group

TABLE 4.12: INTRA GROUP ANALYSIS OF PSFS SCORES- ACTIVITY 3 IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	26.079	<0.001
	Consultation 2 vs. consultation 3	16.303	<0.001
	Consultation 1 vs. Consultation 2	39.820	<0.001

There was a highly significant change over all time points for activity 3 in the active group as shown in Figure 6.

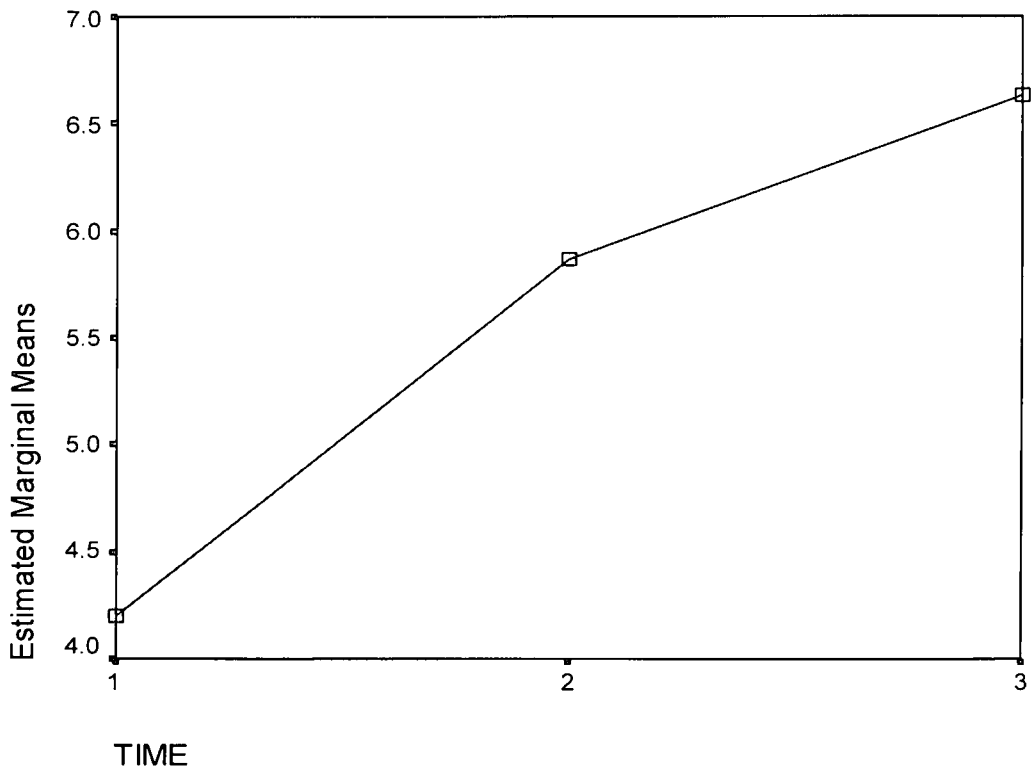

Figure 7: Profile plot of mean PSFS scores- Activity 3 in the active group

TABLE 4.13: INTRA GROUP ANALYSIS OF PSFS SCORES- ACTIVITY 3 IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	13.388	0.001
	Consultation 2 vs. consultation 3	0.798	0.379
	Consultation 1 vs. consultation 3	13.659	0.001

There was a significant change in mean scores for Activity 3 over consultation 1 and 2 but not between consultation 2 and 3 in the placebo group. However an overall improvement was noted between consultations 1 and 3.

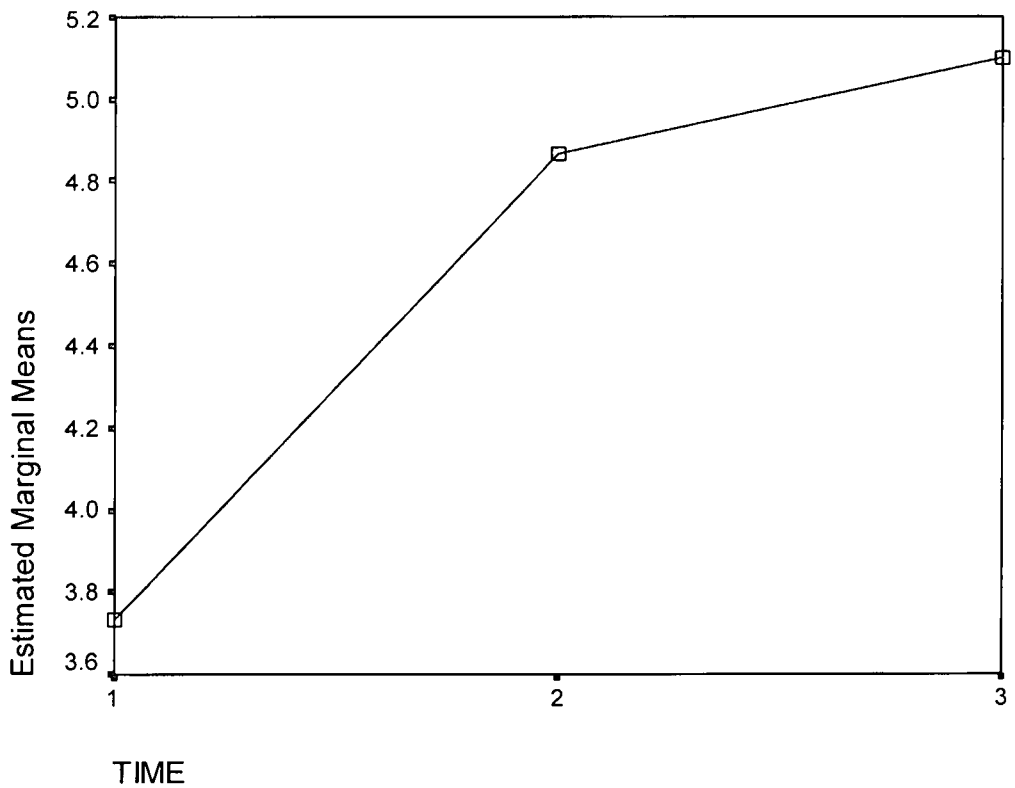

Figure 8: Profile plot of mean PSFS scores- Activity 3 in the placebo group

TABLE 4.14: INTRA GROUP ANALYSIS FOR ALGOMETER READINGS IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	18.019	<0.001
	Consultation 2 vs. consultation 3	28.656	<0.001
	Consultation 1 vs. Consultation 3	38.714	<0.001

Algometer measurements increased significantly ($p<0.001$) over all time periods in the active group.

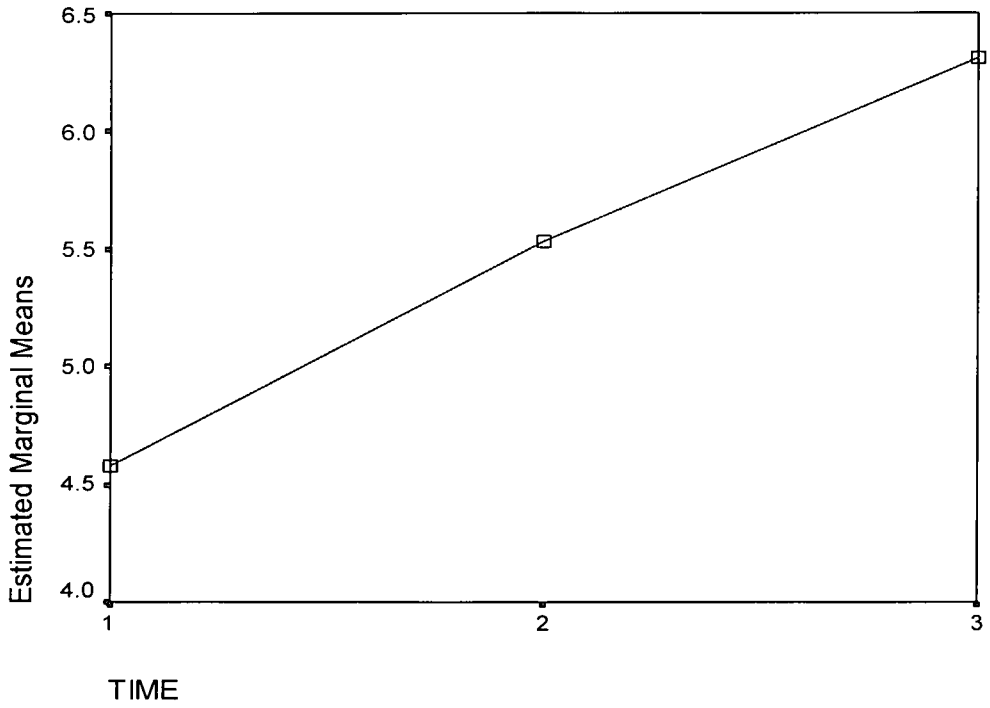

Figure 9: Profile plot of mean algometer readings in the active group

TABLE 4.15: INTRA GROUP ANALYSIS OF ALGOMETER READINGS IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	0.066	0.798
	Consultation 2 vs. consultation 3	0.637	0.431
	Consultation 1 vs. consultation 3	0.058	0.812

There was no significant change in algometer measurements in the placebo group between consultation 1 and 2 (p=0.789), or between consultation 1 and 3 (p=0.812), or between consultation 2 and 3 (p=0.431). Figure 10 shows a general decrease in mean algometer over time in this group.

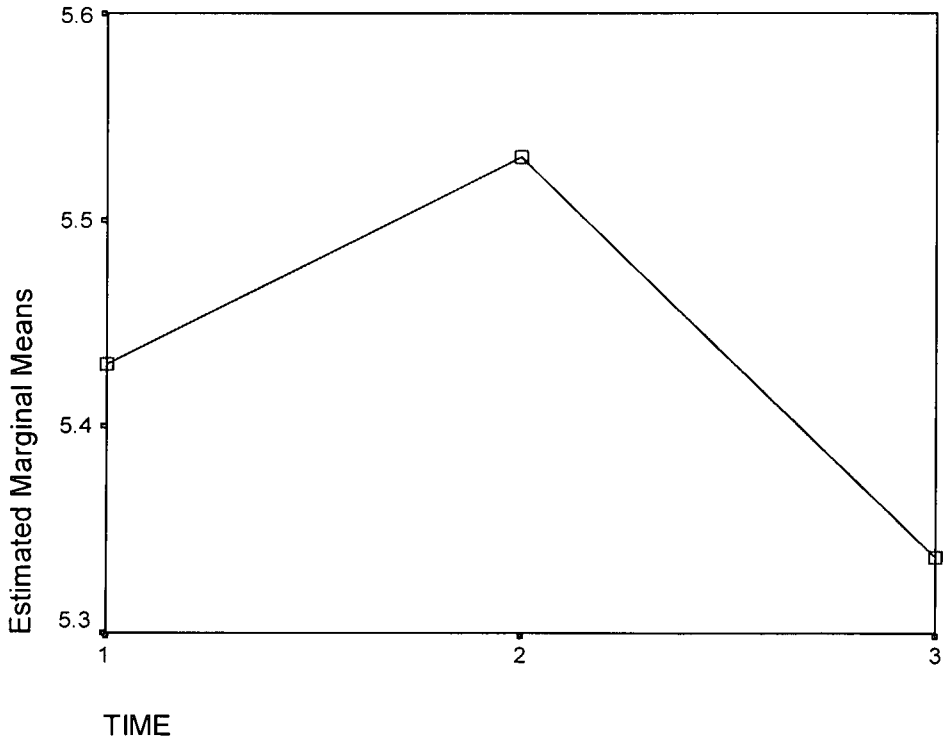

Figure 10: Profile plot of mean algometer readings in the placebo group

TABLE 4.16: INTRA GROUP ANALYSIS OF FLEXION IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	16.898	<0.001
	Consultation 2 vs. consultation 3	15.003	0.001
	Consultation 1 vs. consultation 3	46.374	<0.001

Mean flexion increased significantly over all time periods in the active group as shown in Table 16 and Figure 11.

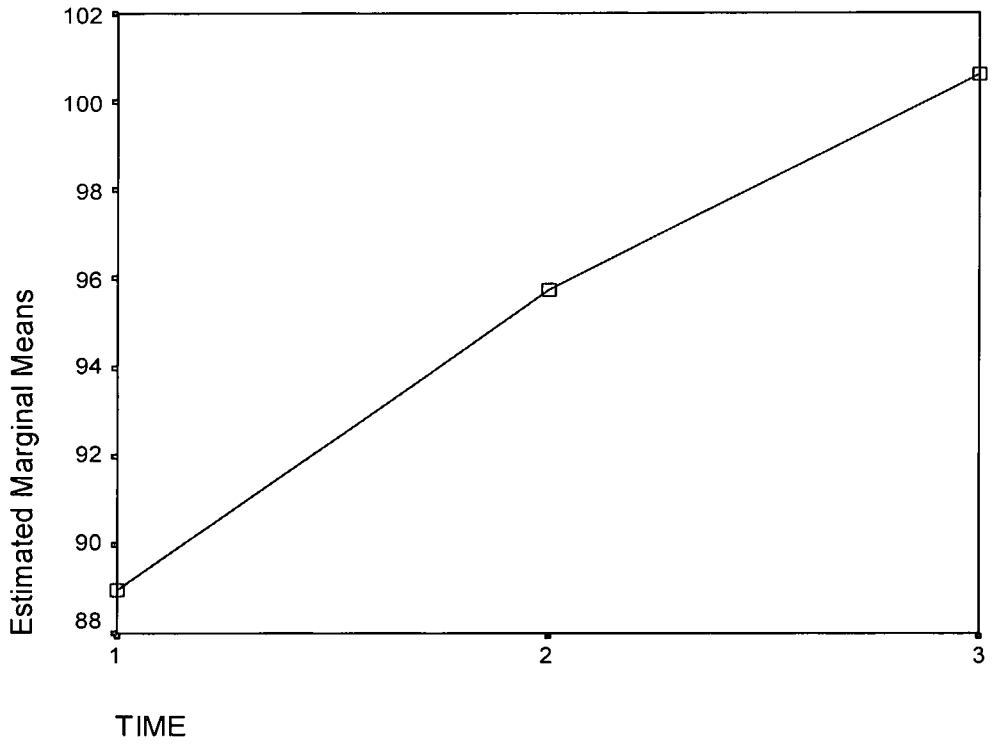

Figure 11: Profile plot of mean flexion readings in the active group

TABLE 4.17: INTRA GROUP ANALYSIS OF FLEXION IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	0.559	0.461
	Consultation 2 vs. consultation 3	0.650	0.427
	Consultation 1 vs. consultation 3	2.428	0.130

The placebo group did not show any significant changes in flexion over all three time periods as shown in Figure 12.

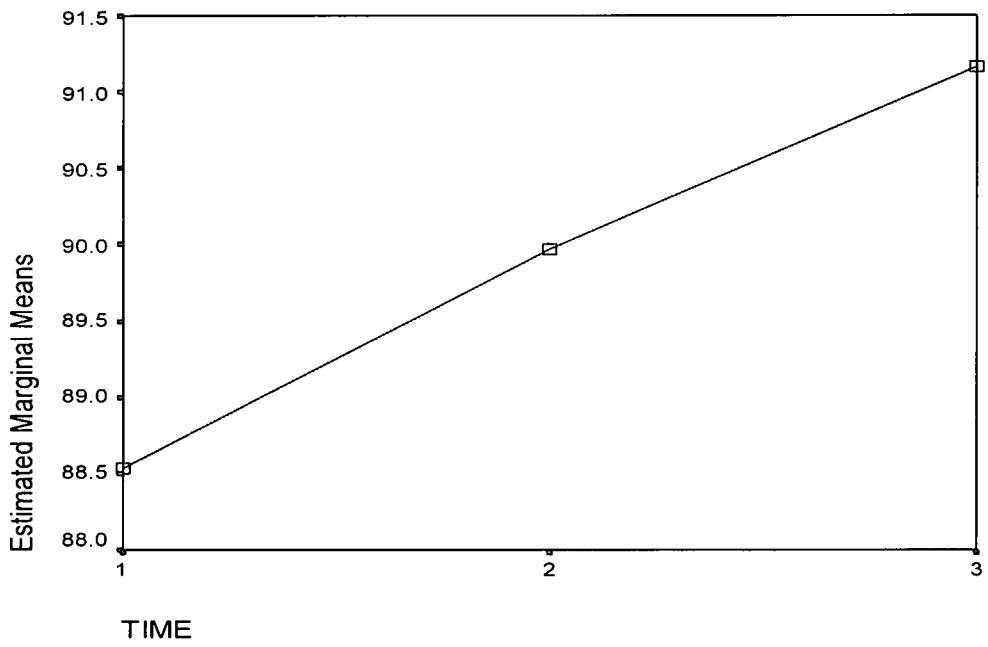

Figure 12: Profile plot of mean flexion in the placebo group over time

TABLE 4.18: INTRA GROUP ANALYSIS OF EXTENSION IN THE ACTIVE GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	23.452	<0.001
	Consultation 2 vs. consultation 3	26.811	<0.001
	Consultation 1 vs. consultation 3	73.500	<0.001

Extension showed a highly significant improvement over all time periods in the active group ($p<0.001$).

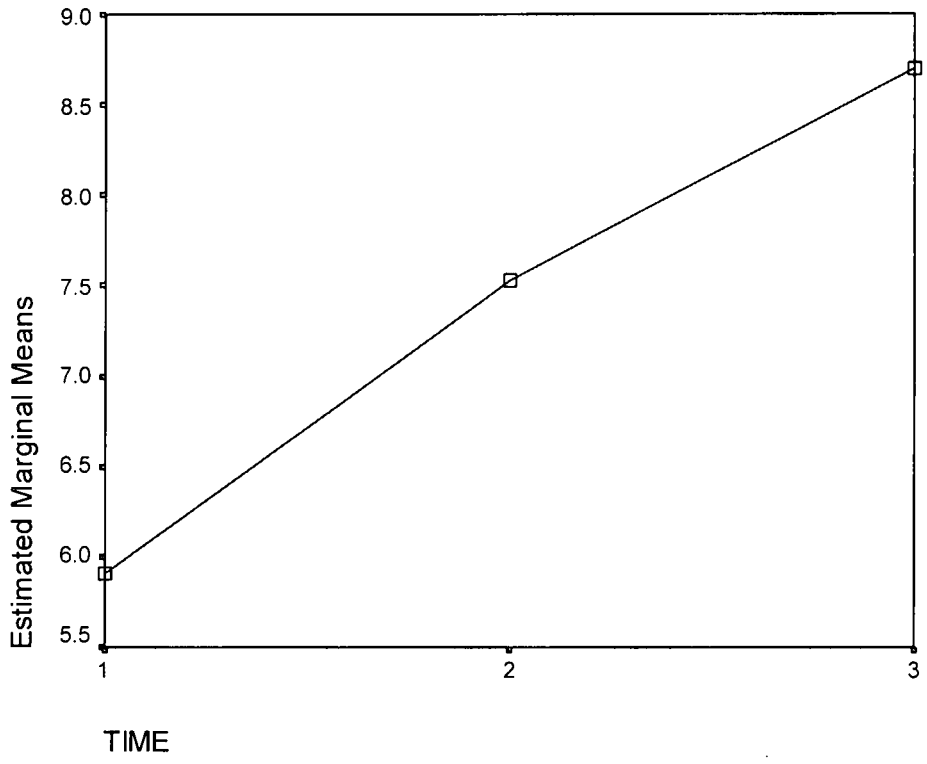

Figure 13: Profile plot of mean extension in the active group

TABLE 4.19: INTRA GROUP ANALYSIS OF EXTENSION IN THE PLACEBO GROUP

SOURCE	TIME PERIOD	F	p value
TIME	Consultation 1 vs. consultation 2	2.377	0.134
	Consultation 2 vs. consultation 3	0.159	0.693
	Consultation 1 vs. consultation 3	2.502	0.125

Extension did not improve significantly over all time periods in the placebo group.

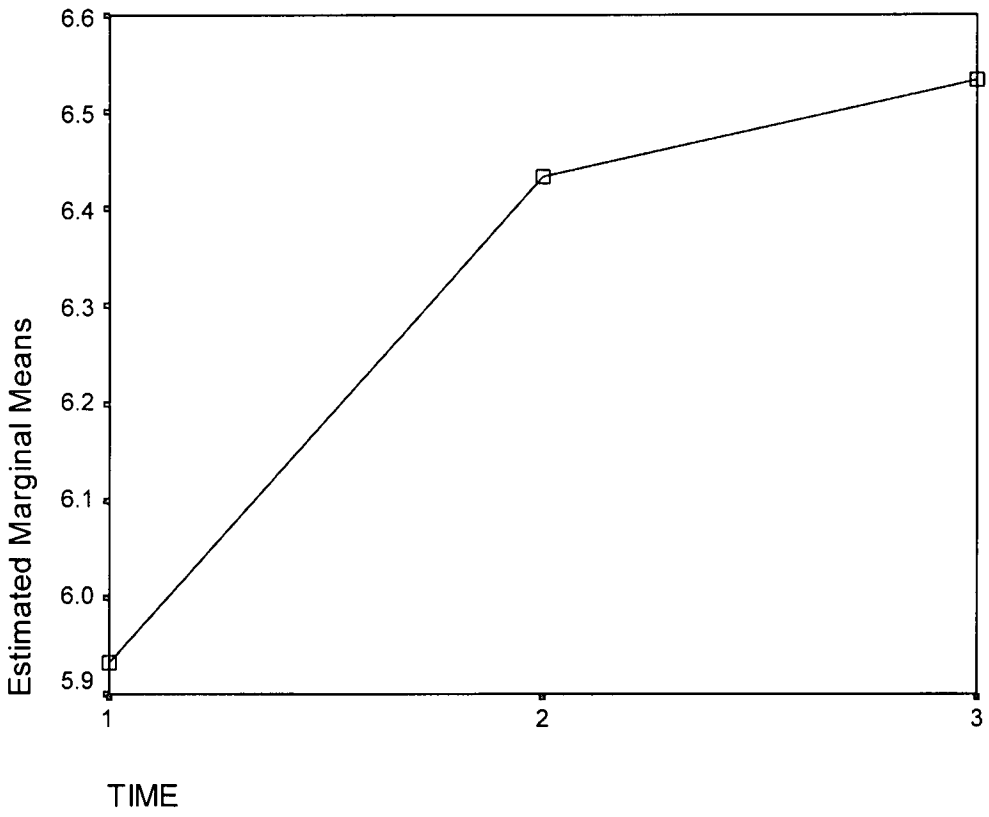

Figure 14: Profile plot of mean extension in the placebo group

4.5 COMBINED INTER AND INTRA GROUP COMPARISON OF TREATMENT EFFECTS

TABLE 4.20: COMBINED OVERALL INTER AND INTRA GROUP ANALYSIS OF TREATMENT EFFECTS FOR NRS SCORES

Effect	Statistic	p value
Time	Wilk's lambda=0.424	<0.001
Time*group	Wilk's lambda=0.908	0.063
Group	F =0.335	0.565

There was a marginally non-significant treatment effect for NRS (p=0.063). The overall time effect was highly significant, in both groups there was a significant decrease in NRS scores over time. Figure 15 shows that although both groups showed a decrease over time, the active group continued to decrease between time 2 and time 3, while the placebo group leveled off. Thus no treatment demonstrated significant differences in improvements between the groups. Therefore we accept the null hypotheses (H_o).

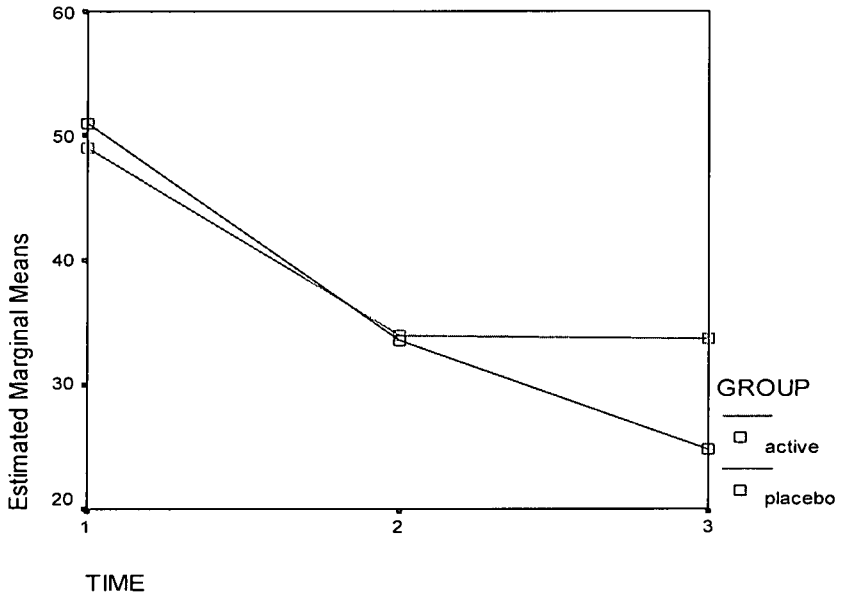

Figure 15: Profile plot of mean NRS scores by group

TABLE 21: COMBINED OVERALL INTER AND INTRA GROUP ANALYSIS OF TREATMENT EFFECTS FOR PSFS SCORES OF ACTIVITY 1

Effect	Statistic	p value
Time	Wilk's lambda=0.449	<0.001
Time*group	Wilk's lambda=0.936	0.153
Group	F =0.018	0.894

Table 21 shows that both groups showed a significant increase in score over time ($p<0.001$). However, the increase over time was not dependant on the treatment group ($p=0.153$), meaning that there was no significant treatment effect. Figure 16 shows that the increase in the active group was at a faster rate than the placebo group, although no significant difference was found. Therefore we accept the null hypotheses (H_o).

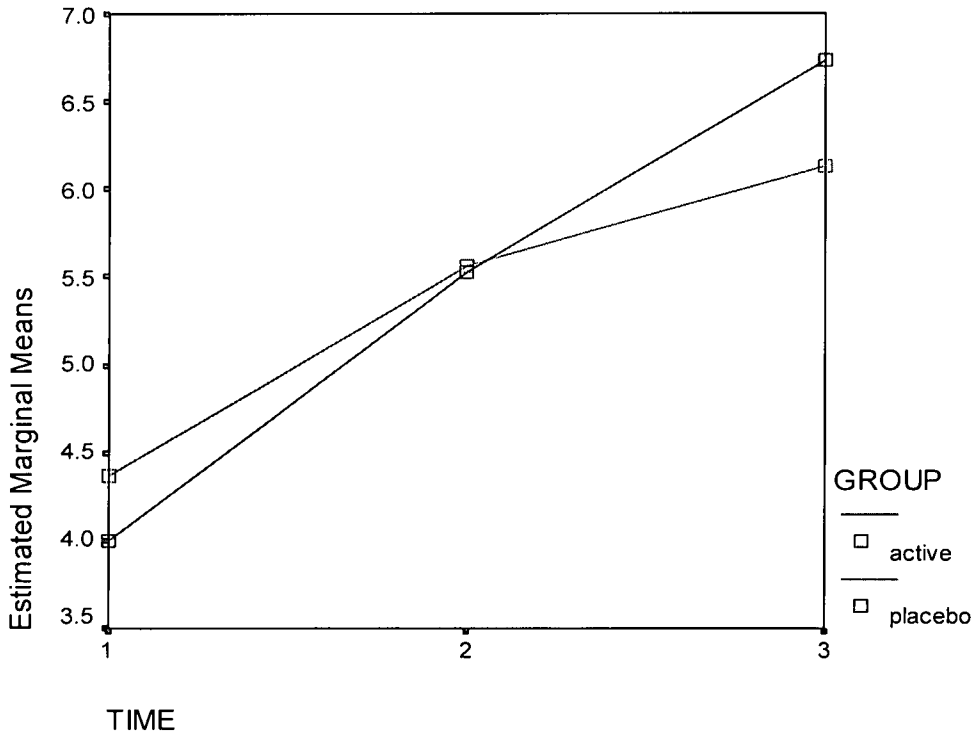

Figure 16: Profile plot of mean PSFS scores- Activity 1 by group

TABLE 22: COMBINED OVERALL INTER AND INTRA GROUP ANALYSIS OF TREATMENT EFFECTS FOR PSFS SCORES OF ACTIVITY 2

Effect	Statistic	p value
Time	Wilk's lambda=0.519	<0.001
Time*group	Wilk's lambda=0.978	0.525
Group	F =2.004	0.162

With the second activity, there was also a highly significant increase in PSFS over time ($p<0.001$). However, both groups increased at the same rate ($p=0.525$). Figure 17 shows that the profiles over time of the two groups were parallel, thus the treatment had no advantage over the placebo for this outcome. Therefore we accept the null hypotheses (H_o).

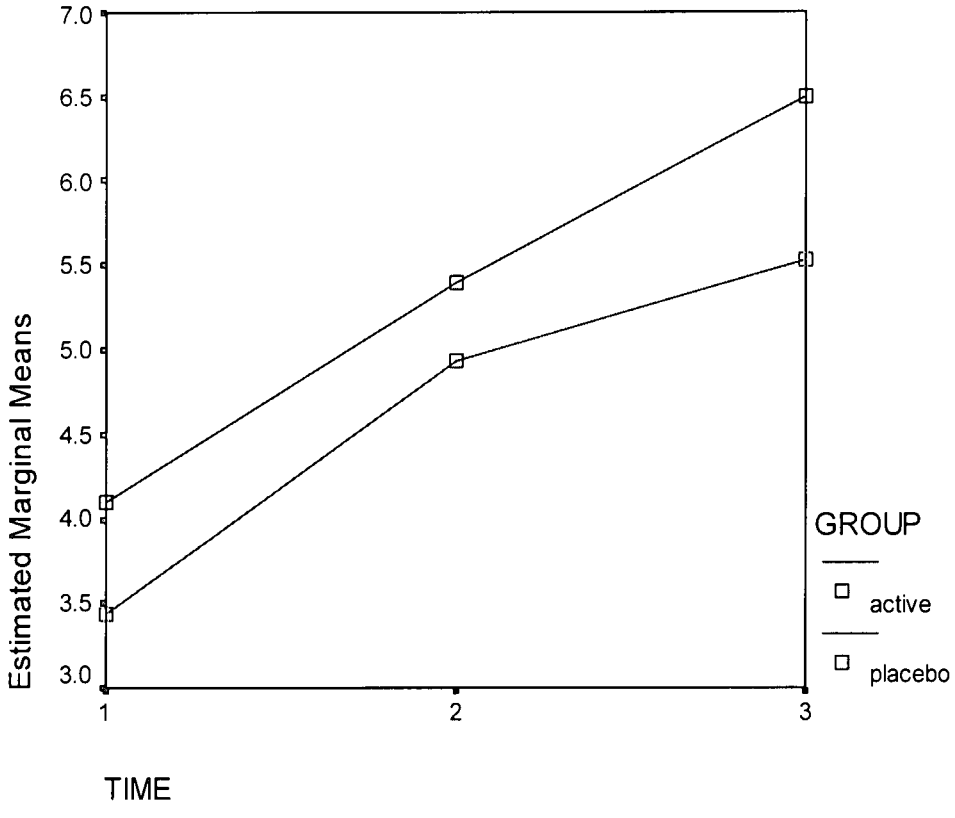

Figure 17: Profile plot of mean PSFS scores- Activity 2 by group

TABLE 23: COMBINED OVERALL INTER AND INTRA GROUP ANALYSIS OF TREATMENT EFFECTS FOR PSFS SCORES OF ACTIVITY 3

Effect	Statistic	p value
Time	Wilk's lambda=0.530	<0.001
Time*group	Wilk's lambda=0.929	0.122
Group	F =3.289	0.075

The third activity also showed significant improvement over time ($p<0.001$), although non significant treatment benefit ($p=0.122$). Figure 18 shows that the profiles were almost parallel although there was a slight trend showing benefit of the active group over and above the placebo group. However, there were no significant differences between the groups. Therefore we accept the null hypotheses (H_o).

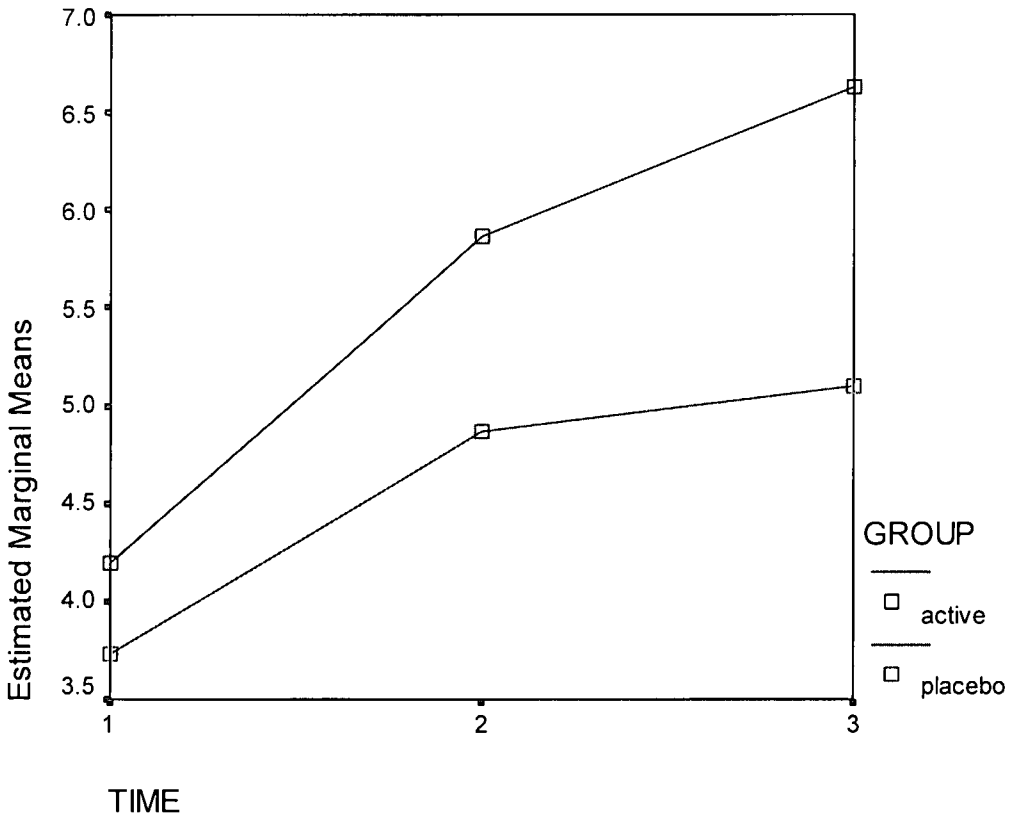

Figure 18: Profile plot of mean PSFS scores- Activity 3 by group

TABLE 24: COMBINED OVERALL INTER AND INTRA GROUP ANALYSIS OF TREATMENT EFFECTS FOR ALGOMETER READINGS

Effect	Statistic	p value
Time	Wilk's lambda=0.825	0.004
Time*group	Wilk's lambda=0.755	<0.001
Group	F =0.011	0.917

There was a highly significant treatment effect for algometer ($p<0.001$). Figure 19 shows that the active group increased at a fast rate while the placebo group remained constant over time. This means that the active treatment was highly effective in comparison to the placebo. Therefore we fail to accept the null hypotheses (H_o) and accept the alternate hypotheses (H_a).

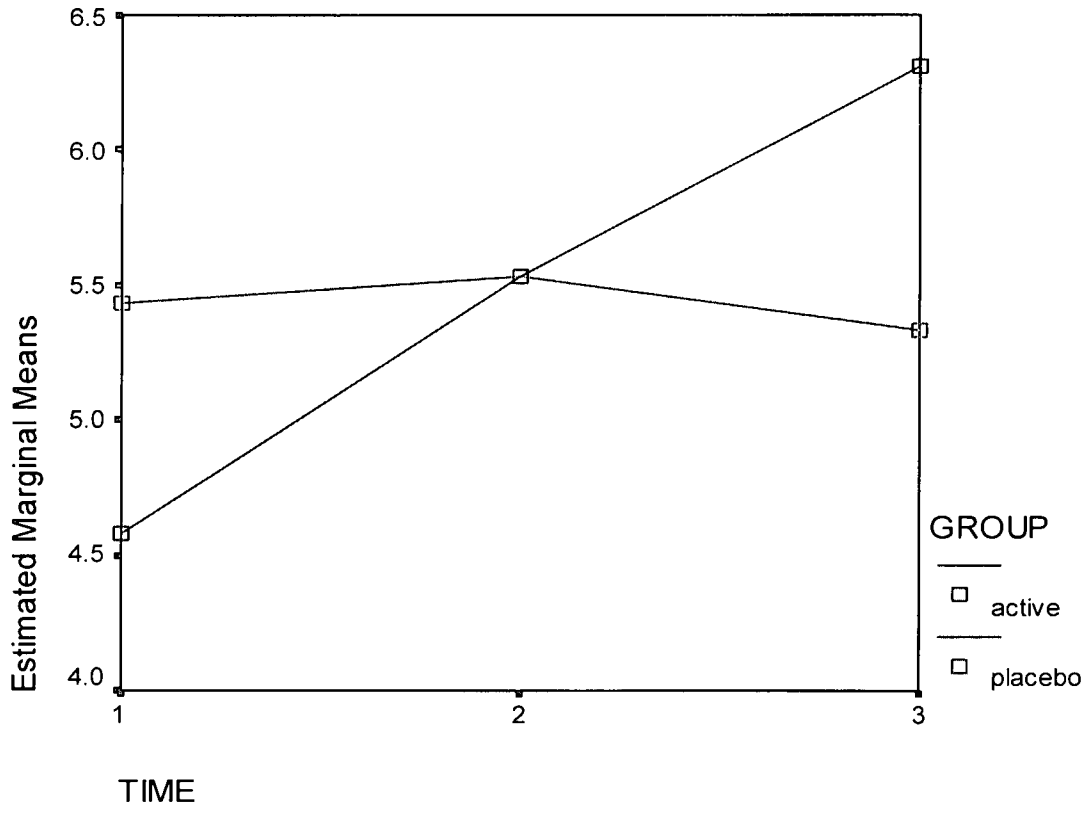

Figure 19: Profile plot of mean algometer readings by group

TABLE 25: COMBINED OVERALL INTRA AND INTER GROUP ANALYSIS OF TREATMENT EFFECTS FOR FLEXION

Effect	Statistic	p value
Time	Wilk's lambda=0.613	<0.001
Time*group	Wilk's lambda=0.801	0.002
Group	F =1.776	0.188

Flexion was significantly better in the active treatment group in comparison to the placebo group (p=0.002). This is shown in Figure 20 where the active group showed a faster rate of increase in flexion over time compared with the placebo. Therefore we fail to accept the null hypotheses (H_o) and accept the alternate hypotheses (H_a).

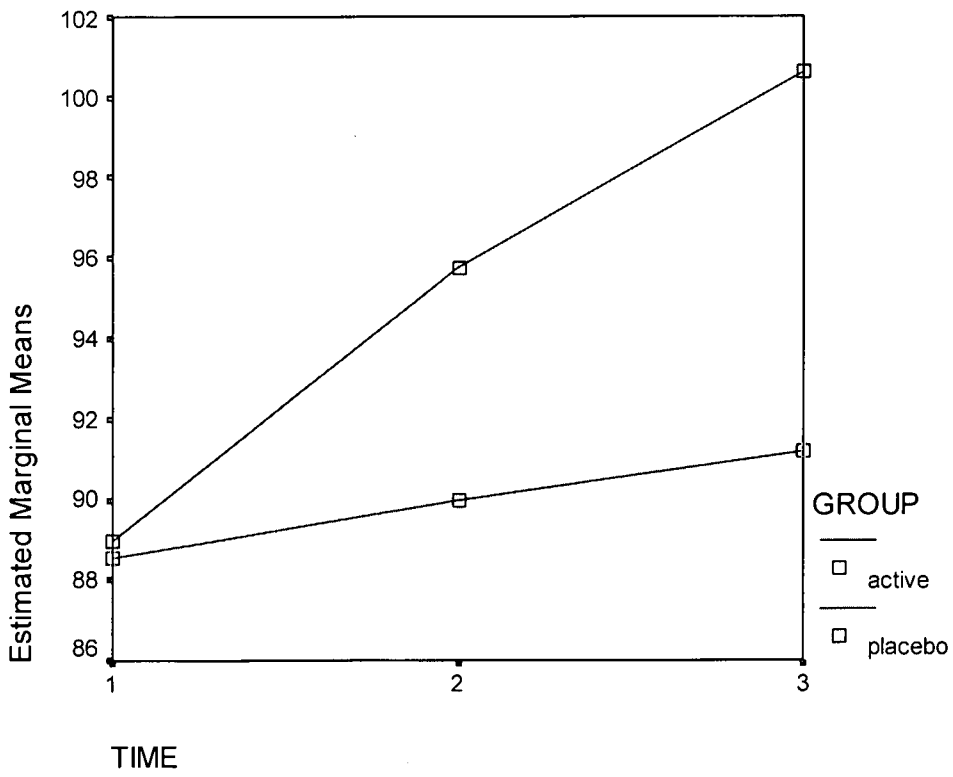

Figure 20: Profile plot of mean flexion by group

TABLE 26: COMBINED OVERALL INTRA AND INTER GROUP ANALYSIS OF TREATMENT EFFECTS FOR EXTENSION

Effect	Statistic	p value
Time	Wilk's lambda=0.552	<0.001
Time*group	Wilk's lambda=0.731	<0.001
Group	F =2.898	0.094

A similar treatment effect was found with extension. The active treatment group improved in extension significantly in comparison to the placebo ($p<0.001$). Figure 21 shows that the rate of increase in extension was faster in the active group than in the placebo group. Therefore we fail to accept the null hypotheses (H_o) and accept the alternate hypotheses (H_a).

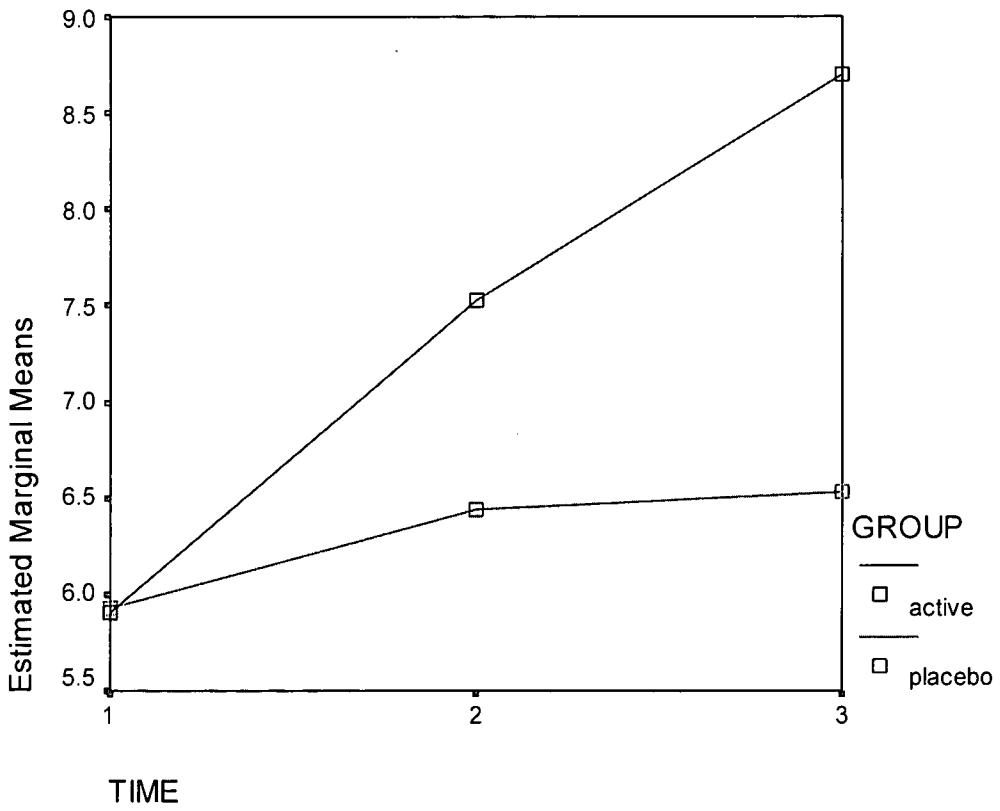

Figure 21: Profile plot of mean extension by group

CHAPTER 5

5.0 DISCUSSION

5.1 INTRODUCTION

This chapter deals with the discussion of the demographic, subjective and objective data presented in Chapter Four.

5.2 DEMOGRAPHIC DATA

Gender distribution analysis (Table 4.1) revealed an overall higher proportion of females (85%) in the sample of sixty, relative to males (15%), however, the distribution of sexes between the groups was the same (p=1.000). The increased female prevalence combined with female age statistics revealing an average age of 57.97, supports the view that postmenopausal hormone deficiency may be a risk factor for DJD and therefore possible knee pain development in women as proposed by Nevitt *et al.* (2001). However, the majority of the women who participated in the study were housewives and probably had the time to participate in the study.

The age distribution (Table 4.2) was not significantly different between the groups (p=0.459). The mean age of the active group was 54.67 and of the placebo group was 53.03 years. These values correlate with findings of Fish, (2002); Robertson, (2001); Tucker, (2001); Nel, (2001) and Naidoo, (2001), where subjects were predominantly over the age of 50. This supports that age is the strongest determinant of DJD and the prevalence of DJD increases with age as mentioned by Creamer and Hochberg (1997). The mechanism underlying these striking age associations might relate to the age-related decline in vascular supply, nutrition of joint tissues or reduced regenerative potential of connective tissue. This might lower resilience to insult which may favor more rapid progression and poor outcome (Brandt *et al.*, 1998). This age related changes may affect chondrocyte turnover, where normal chondrocyte regeneration cannot

compensate the continued chondrocyte destruction which then results in decreased cartilage turnover with further degeneration.

The ethnic distribution (Table 4.3) showed no significant differences between the two groups (p=0.839). Both groups consisted of mainly Indian participants (88.3%), with minor proportions of Whites (6.7%) and Blacks (5%). The increased Indian predominance was probably due to responses from many advertisements placed in Indian residential areas around Durban.

Records were taken on which knee was affected and diagnosed with DJD (Table 4.4). It was the most painful knee that received treatment, and both groups showed that the left knee was the predominantly affected knee (p=0.114). Review of relevant literature did not indicate a specific knee involvement with DJD. The researcher cannot offer a plausible explanation at this stage as to why the left knee was affected in the majority of subjects in this study.

5.3 OBJECTIVE DATA

5.3.1 ALGOMETER READINGS

There was a highly significant treatment effect for algometer readings ($p<0.001$) which favors the active group over placebo group. Algometer readings increased significantly between the first and second consultations and again between the second and third consultations while the placebo group failed to show any statistically significant improvements in algometer readings. We therefore fail to accept the Null Hypothesis (H_o) and accept the Alternate Hypothesis (H_a) which states there would be a significant difference between the two treatment protocols in terms of decreasing tenderness in subjects affected by mild to moderate DJD of the knee.

These findings support the efficacy of the Harpago and celery seed cream in increasing pain threshold. Pain from periarticular structures could have contributed to pain as suggested by Dieppe and Lim (1998). The increase in pain threshold could be due to the pharmacological properties of the Harpago and celery seed cream affecting the associated inflammation in the periarticular structures thereby resulting in reduction of periarticular pain and tenderness which resulted in increased algometer readings. These findings further support the results of the clinical trials conducted by Wegener and Lupke (2003) and Sounderajen and colleagues as cited by Murray (2003) where the oral agents of both the *Harpagophytum procumbens* and the *Apium graveolens* improved pain experienced and mobility.

There were no side effects reported by the subjects during the study. This further promotes the use of the Harpago and celery seed cream over the use of NSAIDs due to the toxicity or common side effects associated with both topical and oral NSAID usage as reported by Ratiner and Lane (2000).

5.3.2 INCLINOMETER READINGS

5.3.2.1 FLEXION AND EXTENSION

There was a highly significant treatment effect for flexion ($p=0.002$) and extension ($p<0.001$) favouring the active group over the placebo group. The active group demonstrated a statistically significant improvement in results for flexion and extension between the first and second consultations and again between the second and third consultations while the placebo group demonstrated no significant improvements in flexion and extension. We therefore fail to accept the Null Hypothesis (H_o) and accept the Alternate Hypothesis (H_a) which states there would be a significant difference between the two treatment protocols in terms of improving range of motion in subjects affected by mild to moderate DJD of the knee.

Reduced range of motion is a feature and an overall contributor to disability, which affects the quality of life of those affected by DJD (O'Reilly and Doherty, 1998). Pain prevents free range of movement, and is at worst at the end of the reduced range (Dieppe and Lim, 1998). It is possible that improvement of flexion and extension in the active group indicates that the Harpago and celery seed cream actually reduced periarticular inflammation resulting in a decrease in tenderness of these tissues. Subjects would have been more willing to move the knee joint through its range of motion if the surrounding tissues were less tender. The decrease in tenderness in the active group is supported by the results of the algometer readings.

5.4 SUBJECTIVE DATA

5.4.1 NRS AND PSFS SCORES

There were no statistically significant treatment effects for NRS scores ($p=0.063$). Both, the active and placebo groups showed a decrease in NRS scores and PSFS scores over time for all three activities ($p=0.153$, $p=0.525$, $p=0.122$). Both the active and placebo groups demonstrated statistically significant improvements in pain and knee function between both consultation periods for all three activities. These results indicate that both treatment protocols were equally effective in improving activities associated with knee function. We therefore fail to accept the Alternate Hypothesis (H_a) and accept the Null Hypothesis (H_o) which states that there would be no difference between the two treatment protocols in terms of decreasing pain and improving subjective activity performance in subjects affected by mild to moderate DJD of the knee.

It is entirely possible that the physiological (e.g. hyperaemia) and psychological (e.g. "a soothing feeling") effects of massage alone could have contributed to pain relief in both groups (Lund, 2000). The Hawthorne effect is another factor

that must be taken into account to explain the results (Mouton, 2002). Subjects, in both groups, irrespective of the intervention they were receiving, could have wanted to please the researcher by giving scores which indicated that they were improving. This could possibly explain why the subjective findings do not correlate with the objective findings in the placebo group. For the NRS and PSFS scores, subjects had access to the data previously recorded as it was contained in their file at every consultation. Subjects may have looked at their previous scores when the researcher stepped out of the consultation room for discussion with a clinician (as is protocol at the Chiropractic Day Clinic at DIT), which could account for improvements noted in both groups.

5.5 COMPARISON TO OTHER STUDIES

The study conducted by Wegener and Lupke (2003), where 75 patients with DJD of the hip and knee were treated with aqueous extracts of the *Harpagophytum procumbens,* was an uncontrolled study which showed minor improvements with respect to WOMAC scores which decreased by 22.9% and VAS pain scores which reduced by 24.5%. The present study, however, was a double-blinded placebo controlled clinical trial which investigated the efficacy of the Harpago and celery seed cream in DJD of the knee only. Results were statistically significant which demonstrated the active treatment group improved in both algometer ($p<0.001$) and inclinometer ($p<0.002$, $p<0.001$) readings.

The improvements noted in this study does support the findings by Sounderajen and colleagues as cited by Murray (2003). A celery extract standardized to contain 85% of celery phthalides had been evaluated in the treatment of degenerative joint disease, osteoporosis and gout. Subjects experienced significant pain relief after 3 weeks of use with the average reduction in pain scores of 68% and some subjects experiencing complete 100% relief from pain. However, their study included patients with gout, DJD and osteoporosis with no specific group allocation with control groups. It is therefore difficult to ascertain

the efficacy of the celery phthalides in reducing pain associated with degenerative joint disease alone.

From the meta-analysis conducted by Mason *et al.* (2004) which reviewed three clinical trials which evaluated the efficacy of oral NSAID's compared to topical NSAID's, it was noted that of the 764 patients included in those trials, 37% had a successful outcome both with topical NSAID's and oral NSAID's. There was no statistically significant difference between the routes of administration (relative risk 1.1; 95% CI 0.9 to 1.3). Side effects did occur in those trials of both oral and topical NSAID's. The efficacy of Harpago and celery seed cream was indicated in this study as subjects improved with respect to pain, tenderness and range of motion and did not suffer any side effects as compared to trials conducted with NSAID's.

According to a trial conducted by Kneusel *et al.* (2002), which investigated the safety and efficacy of an *Arnica montana* fresh plant gel, applied twice daily, in 26 men and 53 women with mild to moderate DJD of the knee. After 3 and 6 weeks, significant decreases in median total scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were evident (both $P < .0001$). Scores on the pain, stiffness, and function subscales also showed significant reductions. The overall local adverse-event rate of 7.6% included only one allergic reaction. Sixty-nine patients (87%) rated the tolerability of the gel as "good" or "fairly good," Topical application of Arnica montana gel for 6 weeks was a safe, well-tolerated, and effective treatment of mild to moderate DJD of the knee. However, the study did not have a control group and this dilutes the significance of the findings of Kneusel *et al.*'s study.

CHAPTER 6

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

This study was a double-blinded placebo controlled clinical trial comprised of a sample size of sixty subjects randomized into two groups of thirty which received either the Harpago and celery seed cream or the placebo cream.

Statistical analysis at $\alpha=0.05$ level of significance revealed both groups improved using subjective measures but no group showed statistically significant differences over the other, however the active treatment group demonstrated significant improvements with an increase in pain threshold and knee flexion and extension as compared to the placebo group.

DJD is still responsible for much pain, disability, and emotional suffering. DJD of the knee requires an integrated treatment regime to assist with symptom relief particularly in the early course of the disease. Due to the fact there are no specific curative mechanisms or agents for this disease, the goal of all therapeutic approaches is aimed at slowing down the arthritic process, alleviating the symptoms experienced and improving the patients' quality of life.

Thus in light of this study's findings, the Harpago and celery seed cream was shown to be a beneficial natural modality for the management of symptoms associated with mild to moderate DJD of the knee.

6.2 RECOMMENDATIONS

The author is of the opinion that with greater time and financial freedom that a study with a larger sample size be undertaken. This would have produced more accurate results in determining treatment efficacy. Homogeneity could also have been improved by taking into account the extent of pain, disability, duration of the patients' symptoms and the specific site of involvement.

Due to the lack of data regarding the rate of uptake and penetration of the surrounding tissues by the Harpago and celery seed cream, future studies are needed to investigate these properties.

As the Harpago and celery seed cream was effective in decreasing pain, tenderness and improving knee range of motion, future studies are needed to investigate its efficacy in comparison to the both oral and topical NSAID's.

An adequate follow-up period i.e. 1 month is recommended. This would provide useful information on the long-term efficacy of the Harpago and celery seed cream in improving symptoms and function.

Subjective data captured during clinical trials should be concealed from subjects to prevent it from influencing their perceptions and outcomes of the study.

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APPENDIX A

DURBAN INSTITUTE OF TECHNOLOGY
CHIROPRACTIC DAY CLINIC
CASE HISTORY

Patient: _____ Date: _____

File # : _____ Age: _____

Sex : _____ Occupation: _____

Intern : _____ Signature _____

FOR CLINICIANS USE ONLY:

Initial visit

Clinician: Signature :

Case History:

Examination:

Previous: Current:

X-Ray Studies:

Previous: Current:

Clinical Path. lab:

Previous: Current:

CASE STATUS:

PTT:	Signature:	Date:

CONDITIONAL:

Reason for Conditional:

Signature: Date:

Conditions met in Visit No:	Signed into PTT:	Date:
Case Summary signed off:		Date:

Intern's Case History:

1. Source of History:

2. Chief Complaint : (patient's own words):

3. Present Illness:

	Complaint 1	Complaint 2
▹ Location		
▹ Onset : Initial:		
Recent:		
▹ Cause:		
▹ Duration		
▹ Frequency		
▹ Pain (Character)		
▹ Progression		
▹ Aggravating Factors		
▹ Relieving Factors		
▹ Associated S & S		
▹ Previous Occurrences		
▹ Past Treatment		
▹ Outcome:		

4. Other Complaints:

5. Past Medical History:

- ▹ General Health Status
- ▹ Childhood Illnesses
- ▹ Adult Illnesses
- ▹ Psychiatric Illnesses
- ▹ Accidents/Injuries
- ▹ Surgery
- ▹ Hospitalizations

6. **Current health status and life-style:**

- Allergies
- Immunizations
- Screening Tests incl. xrays
- Environmental Hazards (Home, School, Work)
- Exercise and Leisure
- Sleep Patterns
- Diet
- Current Medication
  Analgesics/week:
- Tobacco
- Alcohol
- Social Drugs

7. **Immediate Family Medical History:**

- Age
- Health
- Cause of Death
- DM
- Heart Disease
- TB
- Stroke
- Kidney Disease
- CA
- Arthritis
- Anaemia
- Headaches
- Thyroid Disease
- Epilepsy
- Mental Illness
- Alcoholism
- Drug Addiction
- Other

8. **Psychosocial history:**

- Home Situation and daily life
- Important experiences
- Religious Beliefs

9. Review of Systems:

- General
- Skin
- Head
- Eyes
- Ears
- Nose/Sinuses
- Mouth/Throat
- Neck
- Breasts
- Respiratory
- Cardiac
- Gastro-intestinal
- Urinary
- Genital
- Vascular
- Musculoskeletal
- Neurologic
- Haematologic
- Endocrine
- Psychiatric

APPENDIX B

Durban Institute of Technology

PHYSICAL EXAMINATION: SENIOR

Patient Name : _____ **File no :**_____ **Date :**_____

Student : **Signature :**

VITALS:

Pulse rate:			Respiratory rate:	
Blood pressure:	R	L	Medication if hypertensive:	
Temperature:			Height:	
Weight:	Any recent change? Y / N		If Yes: How much gain/loss	Over what period

GENERAL EXAMINATION:

General Impression		
Skin		
Jaundice		
Pallor		
Clubbing		
Cyanosis (Central/Peripheral)		
Oedema		
Lymph nodes	Head and neck	
	Axillary	
	Epitrochlear	
	Inguinal	
Pulses		
Urinalysis		

SYSTEM SPECIFIC EXAMINATION:

CARDIOVASCULAR EXAMINATION

RESPIRATORY EXAMINATION

ABDOMINAL EXAMINATION

NEUROLOGICAL EXAMINATION

COMMENTS

Clinician: **Signature :**

APPENDIX C

DURBAN INSTITUTE OF TECHNOLOGY
Knee regional examination

Patient:_____ File:_____ Date:_____
Intern:_____ Signature:_____
Clinician:_____ Signature:_____

○ **OBSERVATION** (Standing, Seated and during gait cycle).

A. Anterior view
Genu Varum:_____
Genu Valgum:_____
Patellar position:_____
Tibial Torsion:_____
Skin:_____
Swelling:_____

B. Lateral view
Genu Recurvatum:_____
Patella Alta:_____
Patella Baja:_____
Skin:_____

C. Posterior view
Swelling:_____
Skin:_____

D. General
Movement symmetry:_____
Structures symmetry:_____

○ **ACTIVE MOVEMENTS**
Flexion (0 - 135°)_____
Extension (0 - 15°)_____
Medial Rotation (20 - 30°)_____
Lateral rotation (30 - 40°)_____

○ **PASSIVE MOVEMENTS**
Tissue approx_____
Bone-bone_____
Tissue stretch_____
Tissue stretch_____
Patellar movement_____

○ **RESISTED ISOMETRIC MOVEMENTS**
Knee: Flexion:_____
Extension:_____
Internal rotation:_____
External rotation:_____

Ankle: Plantarflexion_____
Dorsiflexion_____

○ **LIGAMENTOUS ASSESSMENT**

One-Plane Medial Instability
Valgus stress (abduction)
Extended_____
Resting Position_____

One-Plane Lateral Instability
Varus stress (adduction)
Extended_____
Resting Position_____

One-Plane Anterior Instability
Lachman Test (0-30°)_____
Anterior Drawer Sign _____

One-Plane Posterior Instability
Posterior "sag" Sign_____
Posterior Drawer Test_____

Anterolateral Rotatory Instability
Slocum Test_____
Macintosh Test_____

Anteromedial Rotatory Instability
Slocum Test_____

Posterolateral Rotatory Instability
Jacob _____
Hughston's Drawer Sign_____
Reverse pivot shift test_____

Posteromedial Rotatory Instability
Hughston's Drawer Sign_____

○ TESTS FOR MENISCUS INJURY

McMurray_____ Anderson med-lat grind_____
"Bounce Home"_____ Apley's_____

○ PLICA TESTS

Mediopatellar Plica _____ Hughston's Plica_____
Plica "Stutter"_____

○ TESTS FOR SWELLING

Brush/Stroke Test _____ Patellar Tap Test_____

○ TESTS FOR PATELLA FEMORAL PAIN SYNDROME

Clarke's Sign _____ Passive patella tilt test_____
Waldron test_____

○ OTHER TESTS

Wilson's_____ Quadriceps Contusion Test_____
Fairbank's_____ Leg Length Discrepancy_____
Noble Compression_____

○ JOINT PLAY

Movement of the tibia on the femur P → A:_____ A → P:_____
Translation of the tibia on the femur M → L:_____ L → M:_____
Long axis distraction of the tibiofemoral joint _____
Inf, sup, lat, + med glide of the patella _____
Movement of the inf. tibiofibular joint A → P_____ P → A_____
Movement of the sup. tibiofibular joint A → P_____ P → A_____
Movement of the sup tibiofibular joint S → I _____ I → S_____

○ PALPATION

Tenderness_____ Swelling_____
Joint line_____ Nodules/exostoses_____
Ligaments_____ Muscles: thigh:_____
Patella:_____ Leg : _____
Patella tendon:_____ Popliteal artery:_____
Bursae:_____

○ REFLEXES AND CUTANEOUS DISTRIBUTION

	R	L
Patellar Reflex (L3,L4)		
Medial Hamstring Reflex (L5,S1)		

○ DERMATOMES

	R	L		R	L
L2			S1		
L3			S2		
L4			S3		
L5					

APPENDIX D

DURBAN INSTITUTE *of* TECHNOLOGY

LETTER OF INFORMATION

Dear participant

Welcome to this study!

Title of the study: A double blinded placebo controlled clinical trial evaluating the efficacy of the Harpago and celery seed cream in the treatment of mild to moderate osteoarthritis of the knee.

Supervisor: Dr J Shaik (031-2042588)

The aim of this study is to evaluate the efficacy of the Harpago and celery seed cream®. Sixty patients will be required to complete the study. Only volunteers will be accepted into this study. These participants will be randomly divided into two treatment groups of thirty each. One group will receive the Harpgo and celery seed cream while the other group will be given a placebo cream.

You will require X-rays of the knee in order to make a diagnosis and to exclude trauma and other pathology. Patients found with severe ligamentous instability of the knee, malignancy or systemic arthritis will be excluded from this study. If you are pregnant or if you think you may be pregnant, you will be excluded from the study due to the possible effects of x-rays and a definite contra-indication to the product being tested.

You will be given a tube consisting of a cream on the initial consultation and will be strictly required to apply and massage a small amount of the cream(the size of a twenty piece on your palm) for about 3-5 minutes by yourself to the affected area twice daily for a period of two weeks. A time sheet will be given to you to record the time of each application. You will also be required to return for two consultations during the two week period.

No physical changes in normal daily routines will be required, and no new exercise regimes may be entered into. There must be no physical changes at work. If you are on any medication we will require a detailed account of the name, the dosage and when the medication is taken.

All consultations will be directed under the supervision of a qualified chiropractor and will be free of charge. You will be free to withdraw from the study at any time. All information will be dealt with in a private and confidential manner.

Thank you

Yours faithfully
Desigan Pillay
(Chiropractic research student)

APPENDIX E

INFORMED CONSENT FORM

(To be completed by patient / subject)

Date : _____ :

Title of research project : A double blinded placebo controlled clinical trial evaluating the efficacy of the Harpago and celery seed cream in the treatment of mild to moderate osteoarthritis of the knee.

Name of supervisor : Dr. Junaid Shaik
Tel : (031) 2042244

Name of research student : Desigan Pillay
Tel : (031) 2042205

Please tick the appropriate answer

		YES / NO	
1.	Have you read the research information sheet?	Yes	No
2.	Have you had an opportunity to ask questions regarding this study?	Yes	No
3.	Have you received satisfactory answers to your questions?	Yes	No
4.	Have you had an opportunity to discuss this study?	Yes	No
5.	Have you received enough information about this study?	Yes	No
6.	Do you understand the implications of your involvement in this study?	Yes	No
7.	Do you understand that you are free to withdraw from this study? at any time without having to give any a reason for withdrawing, and without affecting your future health care.	Yes	No
8.	Do you agree to voluntarily participate in this study	Yes	No
9.	Who have you spoken to? _____		

Please ensure that the researcher completes each section with you
If you have answered NO to any of the above, please obtain the necessary information before signing

Please Print in block letters:

Name of Patient / Subject :_____Signature: _____

Name of witness:_____Signature:_____

Name of Research Intern :_____Signature:_____

APPENDIX F

Numerical Rating Scale - 101 Questionnaire

Date:_____ **File no:**_____ **Visit no:**_____

Patient name: _____

Please indicate on the line below, the number between 0 and 100 that best describes the pain you experience **when it is at its worst**. A zero (0) would mean "no pain at all", and one hundred (100) would mean "pain as bad as it could be".

Please write only **one** number.

0 _____ 100

Please indicate on the line below, the number between 0 and 100 that best describes the pain you experience **when it is at its least**. A zero (0) would mean "no pain at all" and one hundred (100) would mean "pain as bad as it could be".

Please write only **one** number.

0 _____ 100

APPENDIX G

CLINICIAN TO READ AND FILL IN BELOW: Complete at the end of the history and prior to physical examination.

Initial assessment:

I am going to ask you to identify up to three important activities that you are unable to do or are having difficulty with as a result of your_____ problem. Today, are there any activities that you are unable to do or are having difficulty with because of your_____ problem? (Clinician: Show scale to patient and have the patient rate each activity.)

Follow-up assessments:

When I assessed you on (state previous assessment date), you told me that you had difficulty with (read all activities from list at the time). Today do you still have difficulty with: (read and have patient score each item on the list)?

PATIENT – SPECIFIC ACTIVITY SCORING SCHEME (Point to one number):

0	1	2	3	4	5	6	7	8	9	10

Unable to Perform activity

Able to perform activity at same level as before injury or problem

(Date and score)

Activity	Initial	1	2			
1						
2						
3						
4						
5						
Additional						
Additional						

APPENDIX H

INCLINOMETER READINGS

PATIENT NAME:_____

FILE No._____

	CONSULTATION 1	CONSULTATION 2	CONSULTATION 3
FLEXION			
EXTENSION			

APPENDIX I

ALGOMETER READINGS

PATIENT NAME:_____

FILE No._____

	DATE	READING
CONSULTATION 1		
CONSULTATION 2		
CONSULTATION 3		

APPENDIX J

TIME SHEET

NAME:_____

ACTUAL SIZE OF CREAM TO BE APPLIED

DAY	DATE	TIME OF FIRST APPLICATION	TIME OF SECOND APPLICATION
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			

APPENDIX K

Plant species	Harpagophytum procumbens D.C.
Plant material	radix
Extraction medium	30 %(m/m) ethanolum
Drug:native extract ratio	2.6-3,1 = 1 (2,85 = 1)
Drug:extract ratio	2.6-3,1 = 1 (2,85 = 1)
Identity of raw material	Ph.Eur.
Identity of the extract	Flachsmann method
Appearance	light brown, fine powder

Analytical Data

		Specifications	Results
Appearance		see above	complies
Loss on drying (2h, 100-105°C)	%(m/m)	< 5.0	1.6
Bulk density (Ph)	g/ml	0.30 - 0.60	0.30
Harpagoside (HPLC/Ph)	%(m/m)	> 2,10	2.53
Aerobic bacteria (Ph)	/g	< 10000	100
Fungi (Ph)	/g	< 100	< 10
Enterobacteria + other gram-neg.bact.(Ph)	/g	< 100	< 1
Escherichia coli (Ph)	/g	n.d.	n.d.
Staphylococcus aureus (Ph)	/g	n.d.	n.d.
Salmonella (Ph)	/50g	n.d.	n.d.

Ph = Pharmacopoeia tests

n.d. = not detectable

n.t. = not tested

Declaration

Carrier	–
Preservation	–
Residual solvent ethanol	< 0.5%(m/m) (GC/Ph; ICH/283/96, Class 3)
Purity data	The raw plant material complies to:
Pesticide residues	(Form. FA002) Ph.Eur. /2.8.13 resp. RHmV /DFG S-19
Heavy metals	(Form. FA003) Pb, Cd, Hg /AAS
Radioactivity	(Cs134 + Cs137) <370 Bq/kg /Scintillation

Frutarom Switzerland Ltd.
Quality Control
M. Lüönd, Head of QC (valid without sign.) 10.06.2004 / 000021806

APPENDIX L

Durban Institute of Technology: Faculty of Health Research Committee: Ethics

NO.	QUESTION	YES	NO	N/A
	CONFIDENTIALITY			
1.	Does the data collection process involve access to (personal or otherwise) confidential personal data (including access to data for purposes other than this particular research project) without prior consent of subjects? If yes, motivate the necessity.		X	
	COMMENTS			
2.	Will the data be collected and disseminated in a manner that will ensure confidentiality of the data and the identity of the participants? Explain your answer.	X		
	COMMENTS			
3.	Will the materials obtained be stored and ultimately disposed of in a manner that will ensure confidentiality of the participants? If no, explain. If yes specify how long the confidential data will be retained after the study and how it will be disposed of.		X	
	COMMENTS- The data will be kept until it has been analyzed for statistical purposes(4 months) and then only will be disposed of through shredding.			
4.	Will the research involve access to data banks that are subject to privacy legislation? If yes, specify and explain the necessity.		X	
	COMMENTS			
	BENEFITS			
5.	Is this research expected to benefit the participants or organisations directly or indirectly? Explain any such benefits.	X		
	COMMENTS – results of the study will made available to the manufacturers of the product due to their sponsorship of the product for the intended research.			
6.	Does the researcher expect to obtain any direct or indirect financial or other benefits from conducting the research? If yes, explain.		X	
	COMMENTS			

NO.	QUESTION	YES	NO	N/A
	SPONSORS, INTERESTS AND INDEMNITY			
7.	Will this research be undertaken on the behalf of or at the request of a pharmaceutical company, or other commercial entity or any other sponsor? If yes, identify the entity.	X		
	COMMENTS – The House of Health- manufacturers of the Harpago cream.			

8.	If yes to 7, will that entity undertake in writing to abide by Durban Institute of Technology Research Ethics Policy and Guidelines? If yes, do not explain further. If no, explain.	X		
	COMMENTS			
9.	If yes to 8, will that entity undertake in writing to indemnify the institution and the researchers? If yes, do not explain further. If no, explain.	X		
	COMMENTS			
10.	Does the researcher have indemnity cover relating to research activities? If yes, specify. If no, explain why not.	X		
	COMMENTS - The informed consent form which all subjects participating in the study will be required to sign outlines the research process and activities.			
11.	Does the researcher have any affiliation with, or financial involvement in, any organisation or entity with direct or indirect interests in the subject matter or materials of this research? If yes, specify.		X	
	COMMENTS			
12.	Does permission need to be obtained in terms of the location of the study? If yes indicate how permission is to be obtained.		X	
	COMMENTS			
	DECEPTION/COVERT DATA COLLECTION			
13.	Is deception of any kind to be used? If so provide a motivation for acceptability.	X		
	COMMENTS- The use of a placebo(aqueous cream) will evaluate the efficacy of the active ingredients of the Harpago cream as the aqueous cream is an inert cream that does not contain any substances that will affect the results of the study.			
14.	Does the study involve covert data collection? If yes, explain why this is necessary and what steps have been taken to address the ethical implications of this.		X	
	COMMENTS			

RESEARCH ON ANIMALS

15.	Does the research involve the use of animals? If yes, describe the nature of this involvement.		X	
	COMMENTS			

NO.	QUESTION	YES	NO	N/A
16.	Is the research being conducted at an approved facility? If no, explain why. If yes, indicate which facility.	X		
	COMMENTS - The Durban Institute of Technology's Chiropractic Day Clinic.			

RESEARCH ON HUMANS

	RECRUITMENT			
17.	Does recruitment involve direct personal approach from the researchers to the potential subjects? Explain the recruitment process.		X	
	COMMENTS - Subjects will be recruited through advertisements, circulars and handouts.			
18.	Are participants linked to the researcher in a particular relationship, for example employees, students, family? If yes, specify how.		X	
	COMMENTS			
19.	If yes to 18, is there any pressure from researchers or others that might influence the potential subjects to enrol? Elaborate.		X	
	COMMENTS			
20.	Does recruitment involve the circulation/publication of an advertisement, circular, letter etc? If yes, specify and provide copy.	X		
	COMMENTS - Posters and circulars containing information about the research, as well as advertisements in the local newspapers.			
21.	Will subjects receive any financial or other benefits as a result of participation? If yes, explain the nature of the reward, and safeguards.	X		
	COMMENTS- Two free consultations at the Chiropractic Day Clinic at DIT due to the use of a placebo.			
22.	Is the research targeting any particular ethnic or community group? If yes, motivate why it is necessary/acceptable. If you have not consulted a representative of this group, give a reason. In addition explain any consultative processes, identifying participants. Should consultation not take place, give a motivation.		X	
	COMMENTS			
	INFORMED CONSENT			
	Does the research fulfil the criteria for informed consent? [See	X		

23.	guidelines]. If yes, no further answer is needed. If no, please specify how and why.			
	COMMENTS			

NO.	QUESTION	YES	NO	N/A
24.	Will the research involve the use of no-treatment or placebo control conditions? If yes, explain how subjects' interests will be protected.	X		
	COMMENTS - The subjects will be informed of the use of a placebo and will be allowed to withdraw from the study at any time. However to those participating in the study, two free consultations will be offered at the Durban Institute of Technology's Chiropractic Day Clinic on completing the study.			
25.	Will a Subject Information Letter be provided and a written consent be obtained? If no, explain. If yes, attach copies to proposal. In the case of subjects who are not familiar with English (e.g. it is a second language), explain what arrangements will be made to ensure comprehension of the Subject Information Letter, Informed Consent Form and other questionnaires/documents.	X		
	COMMENTS			
26.	Will results of the study be made available to those interested? If no, explain why. If yes, explain how.	X		
	COMMENTS - Results from the clinical trial will be made available to the manufacturers of the Harpago cream(House of Health) in the form of copies of the analysed data from the statistician. However the identity of the participants will be concealed.			
	RISKS TO PARTICIPANTS			
27.	Will participants be asked to perform any acts or make statements that might be expected to cause discomfort, compromise them, diminish self-esteem or cause them to experience embarrassment or regret? If yes, explain.		X	
	COMMENTS			
28.	Might any aspect of your study reasonably be expected to place the participant at risk of criminal or civil liability? If yes, explain.		X	
	COMMENTS			
29.	Might any aspect of your study reasonably be expected to place the participant at risk of damage to their financial standing or social standing or employability? If yes, explain.		X	
	COMMENTS			
30.	Does the research involve any questions, stimuli, tasks,		X	

	investigations or procedures which may be experienced by participants as stressful, anxiety producing, noxious, aversive or unpleasant during or after the research procedures? If yes, explain.			
	COMMENTS			

RESEARCH ON HUMAN HEALTH ISSUES/ BIOTECHNOLOGY

31.	Does the protocol require any physically invasive, or potentially harmful procedures [e.g. drug administration, needle insertion, rectal probe, pharyngeal foreign body, electrical or electromagnetic stimulation, etc]? If yes, please outline below the procedures and what safety precautions will be used.		X	
	COMMENTS			
NO.	**QUESTION**	**YES**	**NO**	**N/A**
32.	Will any treatment be used with potentially unpleasant or harmful side effects? If yes, explain the nature of the side effects and how they will be minimized.		X	
	COMMENTS			
33.	Will any samples of body fluid or body tissues be required specifically for the research that would not be required in the case of ordinary treatment? If yes, explain and list such procedures and techniques.		X	
	COMMENTS			
34.	Are any drugs/devices to be administered? If yes, list any drugs/devices to be used and their approved status.		X	
	COMMENTS			
	GENETIC CONSIDERATIONS			
35.	Will participants be fingerprinted or DNA "fingerprinted"? If yes, motivate why necessary and state how such is to be managed and controlled.		X	
	COMMENTS			
36.	Does the project involve genetic research e.g. somatic cell gene therapy, DNA techniques etc? If yes, list the procedures involved		X	
	COMMENTS			