A Pragmatic Controlled Clinical Trial Investigating the Efficacy of Low-Level Laser Therapy as a Part of the Palliative Management of the Hand Symptoms of Rheumatoid Arthritis.

By:

Keriann Stagg

I, Keriann Stagg, do hereby declare this dissertation to be a true representation of my own work.

___ 14-03-06

Keriann Stagg Date

Approved for final submission by:

___ 14-03-06

Dr. H. Kretzmann (supervisor) Date

14-3-06

Dr. C Korporaal (co-supervior) Date

Dedication

I would like to dedicate this work to God, without Him I could never have made it this far.

> *"O give thanks unto the Lord; for he is good: for his mercy endureth forever"* (Psalms 118: 29)

I would also like to dedicate this work to my family, for their unending love and support, and to Ingrid Adamson for helping to keep me sane.

Acknowledgements

I would like to thank the following people for their advice and assistance, without them my research would not have been possible.

Dr. H. Kretzmann – research supervisor.
Dr. C. Korporaal – research co-supervisor
Mrs. I. Ireland – research administrator.
Mrs. L. Twiggs and Mrs P. Van den Berg – chiropractic clinic administrators.

Lastly I would like to express my gratitude to all the patients who participated in this study, their positive attitudes and perseverance in spite of their chronic illness was an inspiration.

ABSTRACT

The purpose of this pragmatic controlled clinical trial was to investigate the efficacy of low-level laser therapy (LLLT) as a part of the palliative management of the hand symptoms of rheumatoid arthritis (RA). The results were based upon subjective and objective clinical findings.

LLLT may offer a viable treatment option for the hand symptoms of RA as its application theoretically supports and suggests that the physiological effects of LLLT are biostimulation, improved metabolism, increased cell metabolism, improved blood circulation, vasodilatation, analgesic effects, anti-inflammatory and anti-edematous effects; all of which are desired in the treatment of RA (Baxter, 1994; Kahn, 1994, Liggins, 2002).

There is however controversy within the literature as to the efficacy of LLLT (Asada et al., 1991; Bliddal et al., 1987; Goats. et al., 1996; Hall et al., 1994; Heussler et al., 1993; Johannsen et al., 1994; Palmagren et al., 1989; Walker et al., 1987). This is partially attributable to the lack of consensus regarding the methodology applied in these studies.

Other inconsistencies regarding the efficacy of laser in the treatment of RA exist due to the wide range of differing wavelengths and doses that have been used in the published reports, thereby making it difficult to effectively compare studies (Asada et al., 1991; Goats et al., 1996; Hall et al., 1994; Haslett et al., 2001, Heussler et al., 1993; Johannsen et al., 1994; Palmagren et al., 1989; Walker et al., 1987).

This study included a sample of 24 patients with rheumatoid arthritis. They were divided into two groups (Group A and Group B) based on their DASH score and their primary medication. Group A (treatment group) received LLLT of the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints of their more severely affected hand. Patients in Group B (placebo

group) were treated with a laser that was not turned on. Both groups received 9 treatments over 3 consecutive weeks (3 treatments per week). Follow-ups were done the week after the treatments were completed and then again at 1 month.

Subjective measurements were obtained using the Numerical Rating Scale-101 (NRS-101), Disability of the Arm, Shoulder and Hand (DASH) Questionnaire and the duration of morning stiffness. Algometer readings provided an objective measurement.

Data analysis was done using SAS with the repeated measures analysis of variance (ANOVA).
Baseline comparisons between the categorical baseline variables and the group to which the participant was assigned were done using Fisher's exact test. Continuous normally distributed baseline data were compared using the two sample t-test.
A paired t-test was done between the baseline and endpoint to determine whether there was any treatment difference between the two groups.

A graph was drawn of each variable, giving the mean (median) value at each measurement interval for both the treatment and placebo groups.

The results of the study suggest that there was no statistically significant difference in the treatment effect between the treatment and placebo groups The visit effect was statistically significant for most outcomes, meaning that there was a significant improvement from one visit to the next but that neither the placebo nor the laser treatment was significantly more effective than the other.

The treatment group showed better improvement (but not statistically significantly so) for all the outcomes than the placebo did. Therefore, laser therapy may be more effective than the placebo in the management of the hand symptoms of rheumatoid arthritis.

Table of Contents

Chapter Three – Materials and Methods

Chapter Four – Results

List of Appendices

List of Tables

List of Graphs

List of Figures

DEFINITION OF TERMS

Rheumatoid arthritis

- Rheumatoid arthritis is a chronic syndrome characterised by non-specific, usually symmetric inflammation involving the peripheral joints, which may result in progressive destruction of articular and periarticular structures, with or without generalised manifestations (Boers et al., 1999; Yochum et al., 1996).

Cosine law:

- This states that the penetration of rays is directly proportional to the cosine of the angle of incidence (Liggins, 2002).
- Application: The cosine of the angle of incidence is greatest at 90° and therefore the penetration of the ray is greatest if it lies at 90° to the surface.

Law of reflection:

- This states that the angle of reflection equals the angle of incidence (Liggins, 2002).
- Application: The closer the incident ray is to the normal (i.e. 90°) the less the reflection that occurs and therefore the greater the penetration of the ray.

Arndt-Schulz Biological law:

- This states that weak stimuli excite physiological activity; moderately strong stimuli favour it; strong stimuli retard it and very strong ones arrest it (Liggins, 2002).

Inverse square law:

- This states that the intensity of light from a point source falling on a plane surface is inversely proportional to the square of the distance from the source (Kitchen et al., 1996).

Direct contact method:

- The treatment head is applied with a firm pressure directly on the tissue that is to be treated (Kitchen et al., 1996).
- Benefits:
    i. It maximizes the irradiance on the target tissue, which facilitates the effectiveness of laser treatment (inverse square law) (Kitchen et al., 1996).
    ii. It also reduces the risk of accidental exposure of the eyes to irradiation, thus making the treatment inherently safer (Kitchen et al., 1996).

Superoxide dismutase (SOD):

- SOD is an important intracellular enzyme that helps protect against oxygen radical-mediated damage. It appears to be identical to orgotein, which is an anti-inflammatory protein that can be isolated from the liver (Kelly et al., 1993).

Prostaglandin (PG):

- Prostaglandins are produced on demand and are termed local hormones (i.e. they appear to exert their effects on the cell of origin or nearby structures) (Kelly et al., 1993). They are generated by the cycloxygenase pathway and function as inflammatory mediators (Vander, et al., 1998).

Prostacyclin:

- They are a member of the family of prostaglandins produced by endothelial cells.It is a powerful vasodilator and inhibits platelet

aggregation by activating adenylate cyclase, which leads to an increase in intracellular cyclic adenosine monophosphate (cyclic AMP) (Kelly et al., 1993, Novak, 1995).

Acute inflammatory episode:

- The five classic signs of acute inflammation (Kumar et al., 2001):
  i. Rubor (redness)
  ii. Calor (heat)
  iii. Dolor (pain)
  iv. Tumor (swelling)
  v. Functio laesa (loss of function)
- An acute inflammatory episode would be demonstrated by a sudden development or exacerbation of these symptoms in the affected joints during the treatment period.

Cytokines

- These are non-antibody proteins released by certain cells in response to certain antigens, which act as intracellular mediators, as in the generation of an immune system response (Vander et al., 1998).

Interleukin 1 (IL-1)

- This is a cytokine that is secreted by macrophages and other cells. It activates T helper cells, exerts many inflammatory effects and mediates many of the systemic acute phase responses (e.g. fever) (Vander et al., 1998).

Interleukin 6 (IL-6)

- Macrophages and other cells secrete this cytokine. It exerts multiple effects on immune system cells, inflammation and the acute phase response (Vander et al., 1998).

Tumour necrosis factor alpha (TNF-α)

This cytokine kills cells, stimulates inflammation and mediates certain of the systemic acute phase responses (Vander et al., 1998).

CHAPTER ONE

INTRODUCTION

1.1) The Problem and its Setting:

Rheumatoid arthritis (RA) is a chronic syndrome characterised by non-specific, usually symmetric inflammation involving the peripheral joints, which may result in progressive destruction of articular and periarticular structures, with or without generalised manifestations (Boers et al., 1999; Haslett et al. 2001; Yochum et al., 1996).

The early manifestations of RA are usually insidious, with joint pain, stiffness and symmetrical swelling of joints being characteristic. Typically the small joints of the fingers and toes are affected first (Haslett et al., 2001).

The initial hand symptoms of RA are swelling of the metacarpophalangeal joints (MCP), and "spindle-shaped" fingers due to swelling of the proximal interphalangeal (PIP) joints (Haslett et al., 2001). Later volar subluxation (partial dislocation) of the MCP joints and ulnar deviation may develop of the MCP or interphalangeal (IP) joints. Boutonniere and swan-neck deformity of the fingers, Z-deformity of the thumb and arthritis mutilans are also characteristic symptoms of RA (Mody et al., 1989), but are signs of a highly progressed pathogenesis. In addition, the ulnar styloid process may undergo dorsal subluxation, which may contribute to rupture of the fourth and fifth extensor tendons if they are already inflamed (Haslett et al., 2001).

More globally, RA also affects other joints of the body with resultant deformity and dysfunction (Bliddal et al., 1987). In addition to this, the extra-articular manifestations are diverse and include conditions affecting the musculoskeletal system (e.g. tenosynovitis), lymphatic system (e.g. splenomegaly), eyes (e.g. scleritis), cardiac system (e.g. pericarditis), pulmonary system (e.g. fibrosing alveolitis) and the neurological system (e.g. mononeuritis multiplex). Furthermore RA also causes haematological disorders (e.g. anaemia), vasculitis, and amyloidosis with these being represented by systemic manifestations such as fever (Haslett et al., 2001).

In the face of such an extensive clinical picture, the aetiology of RA is still obscure but evidence suggests that the disease may be triggered by TH1 lymphocyte activation and the production of pro-inflammatory cytokines (e.g. IL-1, TNF-α and IL-6). This generally occurs in genetically predisposed individuals with human leukocyte antigen class II haplocytes (Haslett et al., 2001) in response to arthritogenic agents (e.g. Epstein-Barr virus, mycoplasma, parvoviruses and mycobacteria) and results in an autoimmune reaction that damages the joints. Approximately 80% of patients with RA have rheumatoid factors (RFs) which are autoantibodies directed against immunoglobulin G (IgG), present in synovial fluid. Thus RA may be triggered by a combination of genetic and environmental predisposing factors (Kumar et al., 2001).

As a result of the paucity of identified aetiological factors, the treatment of RA is aimed primarily at the relief of symptoms, suppressing the progression of the disease and the conservation and restoration of function in the affected joints (Haslett et al., 2001). This is addressed through the treatment of the patient by drugs, rest, physical therapy and surgery combined with modification of the environment (e.g. aids, appliances, etc).

A wide range of drugs are used in an attempt to effectively manage RA. These include nonsteroidal anti-inflammatory drugs (NSAIDS), which seem to provide important symptomatic relief but do not appear to alter the diseases' long-term course, and salicyclates (a type of NSAID), which are relatively inexpensive drugs with analgesic and anti-inflammatory effects that are used to treat RA. Gold compounds are usually given in

addition to salicyclates and other NSAIDS if these are in themselves insufficient. In addition to these drugs, disease modifying antirheumatic drugs (DMARDS) may also be used in the treatment of the disease (Boers et al., 1999), the most common of which are the corticosteroids. These are the most effective short-term anti-inflammatory drugs used in this condition; however their benefit seems to decrease with time. In addition the use of corticosteroids also needs to be limited due to their side effects for example Cushing syndrome-like features, gastric ulcerations, reactivation of latent tuberculosis, insomnia and osteoporosis (Boers et al., 1999; Haslett et al., 2001).

It is therefore evident that further conservative interventions should be studied in order to assist in the treatment of RA. In this respect low-level laser therapy (LLLT) may offer a viable treatment option as its application theoretically supports and suggests that the physiological effects of LLLT are biostimulation, improved metabolism, increased cell metabolism, improved blood circulation, vasodilatation, analgesic effects, anti-inflammatory and anti-edematous effects; all of which are desired in the treatment of RA (Baxter, 1994; Kahn, 1994, Liggins, 2002).

These clinical effects are based on the fact that diseased or damaged tissues release superoxide radicals, an inflammatory mediator, which combines with arachidonic acid to form prostaglandin E2 (PgE2). This converts adenotriphosphate (ATP) into cyclic adenomonophosphate (cyclic AMP) that in turn results in an increased sensitivity of the nociceptors resulting in increased levels of pain. Irradiation with LLLT results in the release of superoxide dismutase (SOD) that scavenges the superoxide radicals, which decreases the amount of PgE2 produced from the arachidonic acid and ultimately reduces pain (Liggins, 2002).

This effect of LLLT is further enhanced by a photochemical reaction, which converts prostaglandins to prostacyclin endoperoxide with a resultant decrease in the sensitivity of the nociceptors, thus further reducing pain (Liggins, 2002). Furthermore LLLT has been shown in some studies to result in a decrease in the level of perceived pain (Asada et al., 1991; Boers et al., 1999; Heussler et al., 1993; Johansen et al., 1994; Walker et al., 1987).

The reduction in PG-E2 (which promotes inflammation by potentiating the effects of other inflammatory mediators) also results in a decrease in inflammation in the joint. Thus there should also be a decrease in the duration of morning stiffness, which occurs as a result of the accumulation of the inflammatory substances in the joint (Kelly et al., 1993).

In addition to the clinical effects produced by LLLT, the therapeutic application of low-output lasers (<500 mW) in order to treat disease and injury is at dosages that are thought to be too low to cause any detectable heating of the irradiated tissues (Kitchen et al., 1996). In this respect, trials investigating the effects of LLLT, in the treatment of RA, have reported either no side effects or at worse only a burning sensation at the site of irradiation as it is a cold laser therapy (Bliddal et al., 1987).

There is however controversy within the literature as to the efficacy of LLLT (Asada et al., 1991; Bliddal et al., 1987; Goats. et al., 1996; Hall et al., 1994; Heussler et al., 1993; Johannsen et al., 1994; Palmagren et al., 1989; Walker et al., 1987). This is partially attributable to the lack of consensus regarding the methodology applied in these studies. Examples include that of Bliddal et al., (1987) Heussler et al., (1993) and Johannsen et al., (1994), who used the patients' untreated hand as the control in their study. They found a significant decrease in pain in both hands. The improvement in the hand receiving placebo treatment was attributed to disease variance and thus the amount of improvement seen in the placebo hand was then subtracted from that of the treated hand (attributed to the effect of the laser) in order to eliminate disease variance as the cause of the decreased pain. As a result the statistical significance of the improvement in the treated hand disappeared (Johannsen et al., 1994). In addition this protocol disregards the possible systemic effects of laser therapy, which could have had an analgesic effect on the contralateral hand (Baxter, 1994). Other inconsistencies regarding the efficacy of laser in the treatment of RA exist due to the wide range of differing wavelengths and doses that have been used in the published reports, thereby making it difficult to effectively compare studies (Asada et al., 1991; Goats et al., 1996; Hall et al., 1994; Haslett et al., 2001, Heussler et al., 1993; Johannsen et al., 1994; Palmagren et al., 1989; Walker et al., 1987).

As a result, based on the current literature there is a need for the development of a structured approach to the treatment of RA patients for specific or global symptoms.

This research was therefore aimed at determining the efficacy of low-level laser therapy as a part of the palliative management of the hand symptoms of rheumatoid arthritis.

1.2) The Statement of the Problem:

The aim of this study was to evaluate the relative effectiveness of LLLT versus a placebo group in the treatment of the hand symptoms of patients with RA.

The ***first objective*** was to evaluate the relative effectiveness of LLLT versus a placebo in the treatment of the hand symptoms of patients with RA in terms of subjective clinical findings[1].

> ***Hypothesis one:***
> It was hypothesised that if the LLLT is effective there will be a decrease in the readings from both the NRS 101 and the DASH questionnaires.

The ***second objective*** was to evaluate the relative effectiveness of LLLT versus a placebo in the treatment of the hand symptoms of patients with RA in terms of objective clinical findings[2].

> ***Hypothesis two:***
> It was hypothesized that if the LLLT is effective there will be an increase in the algometer reading and a decrease in the duration of morning stiffness.

[1] The subjective measures utilised were the NRS 101 pain rating scale (15), the DASH questionnaire (10) and the duration of morning stiffness.

[2] The objective measure utilised was the algometer readings (5).

1.3) The Rationale of the Study:

1. Rheumatoid arthritis is a chronic, relapsing multi-systemic disabling and debilitating condition for which there is no cure (Shaik, 2003). Therefore the various options of treatment need to be researched.
2. Standard treatment options (e.g. corticosteroids and NSAIDS) have positive short term effects but their long term use needs to be limited due to their side effects (Bliddal et al., 1987; Haslett et al., 2001). There is therefore a need to investigate other treatment modalities, which have fewer side-effects, in terms of their medium and long term effects on rheumatoid arthritis
3. LLLT has physiological effects (e.g. analgesia, anti-inflammatory and anti-oedematous effects), which may prove to be effective in the management of rheumatoid arthritis (Liggins, 2002).
4. Trials investigating the effects of low- level laser therapy have reported no side effects or at worse only a burning sensation at the site of irradiation (Johannsen et al., 1994).

1.4) Benefits of the study:

The potential implications of this study depend on the final results obtained. If LLLT were found to be effective in managing the hand symptoms of RA it would mean that it could provide an additional facet to the multi-disciplinary management of RA, by decreasing the pain, swelling and morning stiffness experienced by patients in their hands. Thus it would improve their functional daily ability and enhance their self-sufficiency in both self-care and vocational activities. The inability of medications to completely alleviate the symptoms of inflammation of a joint means that there is a definite need for adjunctive treatment options to further decrease these symptoms as much as possible. LLLT, if found to be effective, would contribute to this and since it has been found to have little or no side effects it would be a sound choice as a treatment option.

If LLLT were not found to be effective in this research, it would mean that other potential laser parameters might need to be investigated, as they might differ in their therapeutic value. It would also create a need for practitioners to utilise other proven treatment modalities in the management of RA instead of using LLLT.

1.5) Limitations of the study:

Despite every attempt made to construct a parameter bound research design, there are certain inherent limitations that cannot be controlled for. It was therefore necessary to assume the following,

1. That each patient has been completely transparent when recording his or her subjective data (NRS 101, DASH questionnaire and duration of morning stiffness). As patients may either consciously or unconsciously be inaccurate in their recordings and therefore it was impossible to assume complete open and honest responses to all the questions by every patient. In other words, the Hawthorne effect may have had an influence on the results (Mouton, 2002; Bailey, 1997).
2. That the patients who were placed in any given category (e.g. severe functional limitation), based on the score of their DASH questionnaire, were at the same point in the pathogenesis of their RA. This was not always true and was thus an intrinsic limitation.
3. That the patients placed in any given sub-category (e.g. NSAIDS), based on their primary medication, were not experiencing any drug-interactions between their primary medication and any other medications that they were taking concurrently for either their RA or unrelated conditions (e.g. hypertension). These drug-interactions are highly variable and could not be excluded in any patient and therefore constituted a limitation in terms of the ability of the researcher to assess these parameters.
4. That the patients' symptoms were not being exacerbated by any unavoidable external factors (e.g. weather or diet) which some individuals may have been sensitive / exposed to whilst others were not during the course of their normal daily

activity. This reactivity could be reduced if the exposure to the external factor(s) was maintained throughout the study for any one particular individual.

5. That the patients did not have any other undiagnosed medical condition that may have influenced their symptoms attributed to RA (e.g. pain or morning stiffness), which would have been masked by the clinical presentation of RA and therefore not readily detectable through a case history or physical assessment of the patient for purposes of this research.

1.6) Summary:

In order to elaborate on the study, Chapter two will give an overview of the syndrome under study as well as the current treatments available, with Chapter three indicating the materials and methods applicable to this study. Chapter four presents the results obtained from the statistical analysis of the clinical outcome measures, while chapter five discusses the trends observed in the results. Chapter six completes the dissertation with the conclusions of this study and recommendations for future studies in this field.

CHAPTER TWO

LITERATURE REVIEW

2.1) Introduction:

The purpose of this chapter is to highlight relevant literature regarding information on rheumatoid arthritis specifically as it affects the hands, and the management of this condition using LLLT.

2.2) Anatomy of Synovial joints:

In order to more comprehensively understand the pathology, pathogenesis and clinical presentation of RA, the anatomy of the synovial joint becomes important and therefore the initial portion of this chapter will discuss the anatomy of these joints, with particular reference to the hand.

Synovial joints possess certain features that make them unique, namely (Yochum et al., 1996):

- a joint capsule,
- articular cartilage,
- synovial membrane and fluid,
- joint space and
- opposing smooth bony surfaces

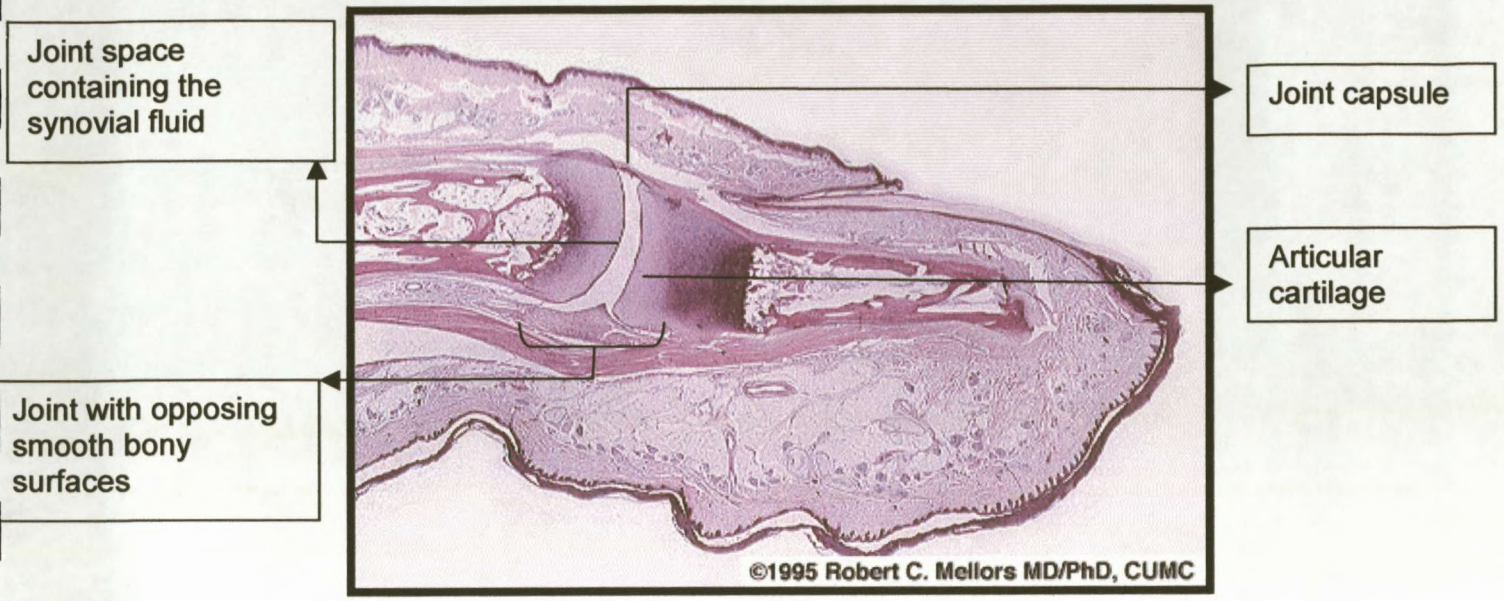


Figure 2.1: Histology

Adapted from :

http://edcenter.med.cornell.edu/cumc PathNotes/Skeletal/JOINTLIST.html

The ***joint capsule*** is fibrous in nature and fulfills a function similar to that of a ligament. The fibers of the capsule are continuous with and penetrate the adjacent periosteum. There are varying amounts of intracapsular bone depending on the specific joint and in some joints there may be a fibrocartilaginous disc extending into the joint from the capsule (Yochum et al., 1996).

The ***synovial membrane***, which consists of loose, vascular connective tissue, lines the fibrous capsule and non-articular bone and secretes synovial fluid (Moore et al., 1999). The cartilage is almost completely absent on the nonarticulating intraartiular bone, resulting in the so-called "bare areas". At the junction between the bone and cartilage there are interdigitations, which allow for adequate adherence between the two tissues (Moore et al., 1999). The so called "bare areas", where the synovium lies in direct contact with intra-articular bone, are predisposed to bone erosion from synovial disease (Yochum et al., 1996). Due to its relatively avascular nature, the cartilage is dependent on the synovial fluid for its nutrition (Yochum, et al., 1996).

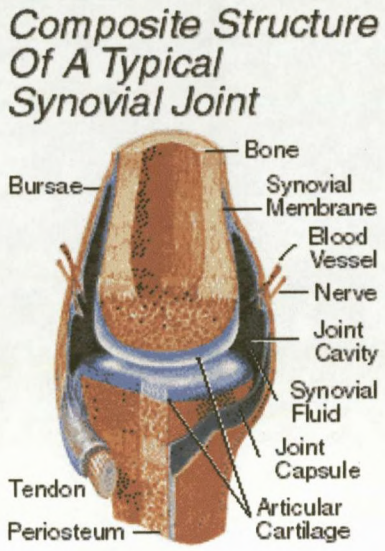


Figure 2.2: A Typical Synovial Joint

Adapted From:

http://www.vaxa.com/images/634a.gif

Synovial fluid is a dialysate of blood plasma that passes into the extracellular space, through the fenestrations of subsynovial capillary endothelium, where it joins with hyaluronic acid that is secreted by synovial cells. The oncotic pressure of synovial fluid is related to the quantity of plasma proteins and hyaluronic acid present in the fluid (Kelly et al., 1993).

In addition the intra-articular pressure is also influenced by the rate of egress of fluid from the joint. Slight decompression helps pump the venous return and maintains an arterial-venous pressure lower than that in the adjoining collecting system. This combined with a similar mechanism in the lymphatic system clears extravascular plasma proteins from the synovium, thus lowering the oncotic pressure and promoting fluid passage (Kelly et al., 1993).

The function of synovial fluid is to provide lubrication and nutrition for the joint (Yochum et al., 1996). There are at least 12 proposed mechanisms by which joint lubrication can be explained, however most fall into these two categories:

- ☑ Fluid-film lubrication (surfaces are separated by a fluid film) and
- ☑ Boundary lubrication (there is protection and decreased friction between surfaces due to special molecules attached to the cartilage surface) (Kelly et al., 1993).

The most common type of ***intraarticular cartilage*** is hyaline cartilage. It is made up of chondrocytes lying within a matrix of collagen fibrils and a mucopolysaccaride ground substance. The thickness of the cartilage ranges between 1mm and 7mm, depending on the joint involved. Generally the greater the stress placed on the joint, the thicker the cartilage (Yochum et al., 1996).

Adult articular cartilage is avascular in nature and the morphologic, physiologic and pathologic studies looked at by Kelly et al., (1993) have confirmed that solutes pass from the synovial fluid into cartilage. There are three potential mechanisms for nutrient transfer with in the cartilage matrix, namely:

- ☑ diffusion,
- ☑ active transport by chondrocytes and
- ☑ pumping by intermittent compression of the cartilage matrix.

Therefore articular cartilage has a limited ability to repair itself and only functions effectively for the lifetime of the individual if the physical demands placed on it are kept within a narrow range (Kelly et al., 1993).

The subchondral bone (i.e. the bone that underlies the articular cartilage) is made up of a thick cortex and underlying cancellous bone. This bone has an abundant blood supply and is metabolically active. There is generally no periosteum lining the intracapsular bone (Yochum et al., 1996).

The ***joint space and the opposing joint surfaces*** interact as the last feature of the synovial joint, were these may be further classified according to the type of function that is required based on the bony morphology of the joint. There are thus 6 major types of synovial joints (Moore et al., 1999):

- ☑ plane,
- ☑ hinge,
- ☑ saddle,
- ☑ condyloid,
- ☑ ball and socket and
- ☑ pivot joints.

When looking at patients with rheumatoid arthritis, it is important to note that anatomy related to the ***PIP*** (proximal interphalangeal joint) and ***DIP*** (distal interphalangeal joint). These joints are hinge joints, which move in one plane (sagittal) around a single axis thereby allowing only flexion and extension. Therefore the articular cartilage of hinge joints is lax and thin posteriorly and anteriorly where movement occurs. Relatively strong collateral ligaments join the two articulating bones to each other (Moore et al., 1999).

In contrast to this the ***MCP*** joints are biaxial and allow movement in two planes (sagittal and coronal), movement in one axis (sagittal) is usually greater than in the other. Condyloid joints allow flexion, extension, abduction and adduction (Moore et al., 1999).

However both of these joints have been implicated in joint pathology associated with rheumatoid arthritis whose pathology is discussed below.

2.3) Pathology:

The aetiology of rheumatoid arthritis is unclear; however evidence suggests that the disease may be triggered by TH1 lymphocyte activation and the production of pro-inflammatory cytokines (eg IL-1, TNF-α and IL-6) in genetically predisposed individuals with human leukocyte antigen class II haplocytes (Haslett et al., 2001). This occurs in response to

arthritogenic agents (e.g. Epstein-Barr virus, mycoplasma, parvoviruses and mycobacteria) and results in an autoimmune reaction that damages the joints (Haslett et al., 2001).

Most of the effects of interleuken-1 (IL-1) on cells are associated with stimulation of prostaglandin (PG) production and inflammation. Evidence suggests that prostaglandin E2 (PG-E2) assists in the development of inflammation more through its role of potentiating the effects of other inflammatory mediators than by it directly inducing inflammation. PG-E2 increases pain sensitivity to bradykinin and histamine and evidence suggests that it (and not PG-E1) markedly enhances the chemotactic responsiveness of human monocytes to complement-activated human serum (Kelly et al., 1999).

PG-E2 is also the most potent stimulator of bone resorption among the prostaglandins (PG's). The bone resorption is complement dependent and prostaglandin mediated. This may help to explain the bony erosion that occurs in the joints of patients with RA where complement is activated and PG-E2 concentrations are high (Kelly et al., 1999).

The earliest change seen in rheumatoid arthritis is congestion and swelling of the synovial membrane and the underlying connective tissue. These become infiltrated with macrophages, lymphocytes (especially CD4 T cells) and plasma cells (Haslett et al., 2001). Activated CD4 T cells produce cytokines that have two main effects:

- ❖ firstly to activate the macrophages and other cells in the joint space and
- ❖ secondly to activate B-cells.

The activated macrophages release tissue-destructive enzymes and other substances that perpetuate the inflammation. The activated B-cells produce antibodies, some of which are directed against the joints. Approximately 80% of individuals with rheumatoid arthritis have rheumatoid factors (RFs) which are autoantibodies directed against immunoglobulin G (IgG), present in synovial fluid (Kumar et al., 2001).

During the active phase of the disease there is effusion of synovial fluid into the joint space. The synovial membrane hypertrophies and lymphoid follicles, which resemble an immunologically active lymph node form (Haslett et al., 2001).

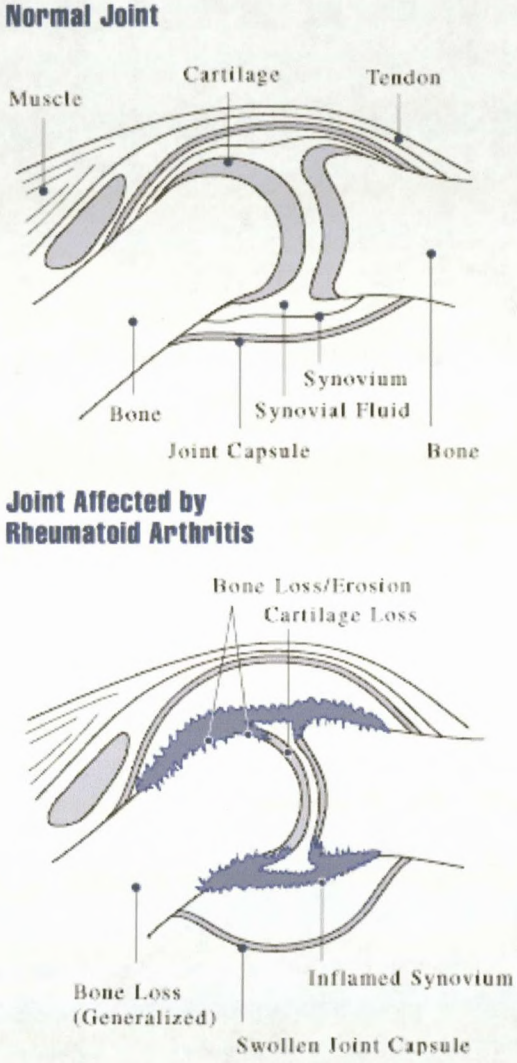


Figure 2.3: A Joint affected by Rheumatoid Arthritis

Adapted From:

http://upload.wikimedia.org/wikipedia/en/thumb/7/7e/Rheumatoid_arthritis_joint.gif/180px-Rheumatoid_arthritis_joint.gif

Pannus (an inflammatory granulation tissue) progressively destroys the articular cartilage as it spreads over and under it. Later the joints may undergo fibrous or bony ankylosis. The

muscles situated adjacent to the inflamed joints atrophy and may also be infiltrated by lymphocytes (Haslett et al., 2001).

2.4) Epidemiology:

In White populations the overall prevalence of rheumatoid arthritis globally is about 1% and the annual incidence of new cases is approximately 200 per million per year (Haslett et al., 2001). The prevalence of rheumatoid arthritis in urban Black populations in South Africa is similar to that in the White population (Mody et al., 1989). Studies conducted in 1961 and 1975 noted that there was a dramatic increase in the prevalence of RA in urban black South Africans as compared with rural black South Africans (Kelly et al., 1999). A study conducted in 1989, however, found that the prevalence of RA in the urban Black population did not differ significantly from that in the rural population surveys in the Transkei and Lesotho (Mody et al., 1989). Nevertheless it was noted that Black Africans were noted to have an unusually high incidence of severe erosive disease (Kelly et al., 1999).

The onset typically occurs between the ages of 20 and 60 years with the peak being between 40 and 50 years of age (Haslett et al., 2001).

Internationally the female to male ratio in the 20 to 40 year age group is 3:1 whereas after 40 years of age the ratio is approximately 1:1 (Yochum et al., 1996). There are no differences in terms of clinical signs, severity or radiographic changes between the sexes (Yochum et al., 1996). These ratios are in contrast to the female to male ratio in South Africa that has been estimated at approximately 3.7:1(Mody et al., 1989).

2.5) Clinical presentation – signs and symptoms:

The onset of rheumatoid arthritis in 50 to 75% of the cases is insidious, occurring over weeks or months. The initial symptoms may be systemic or articular and although symmetric

involvement is common, an initially asymmetric presentation is not unusual (Kelly et al., 1999). The initial articular symptoms usually include pain, stiffness and symmetrical swelling of joints (Haslett et al., 2001).

In 8 to 15% of the patients the onset is acute and occurs within a matter of days. Symptoms mount, with pain starting to occur in other joints. The joint involvement is often less symmetric than that seen when the onset is insidious. In cases where the onset is acute, the diagnosis of RA can be difficult and sepsis or vasculitis must first be excluded (Kelly et al., 1999).

Finally, 15 to 20% of patients have an intermediate type of onset. In these cases the symptoms develop over days or weeks and systemic complaints are more noticeable than in the insidious type of onset (Kelly et al., 1999).

The most common joints affected in the early stages of RA are the MCP joints, PIP joints and the wrists (Haslett et al., 2001; Kelly et al., 1999)

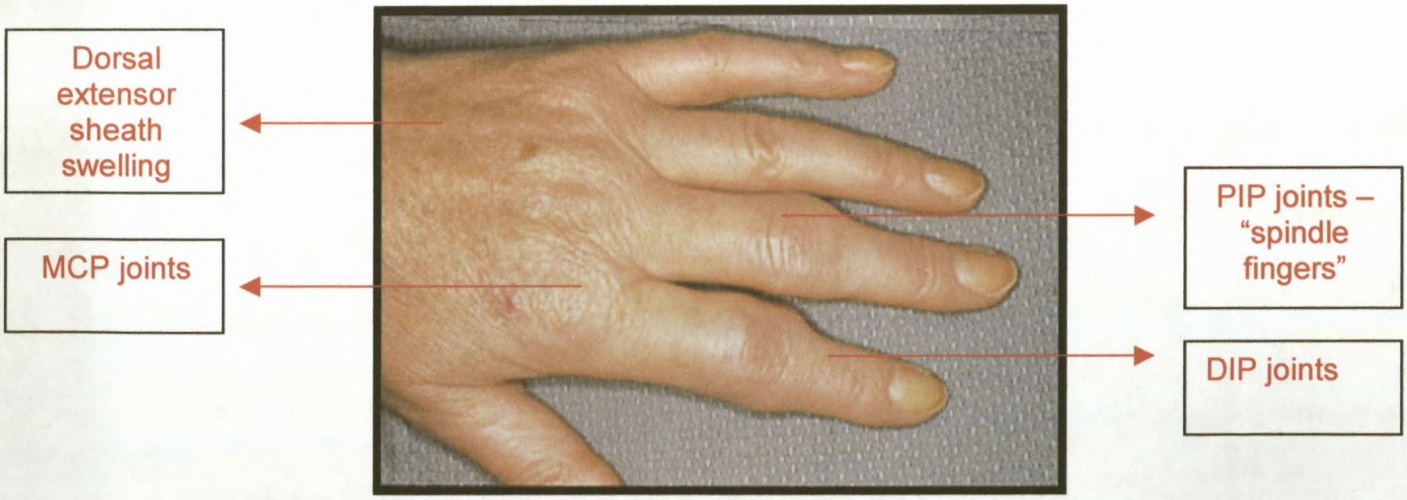


Figure 2.4: Hand Showing Spindle Fingers

Adapted from

http://www.hopkins-arthritis.som.jhmi.edu/rheumatoid/images/clinical/phyex1b.jpg

The initial hand symptoms of rheumatoid arthritis are swelling of the MCP and "spindle-shaped" fingers due to swelling of the PIP joints (Haslett et al., 2001).

Swelling of the dorsal aspect of the wrist within the tendon sheaths of the extensor muscles is one of the earliest signs of RA. The most commonly involved sheaths are those of the extensor carpi ulnaris and extensor digitorum. In rare instances, cystic structures resembling ganglia are early findings of RA (Kelly et al., 1999).

Pressure increases in the relatively non-distensible joint spaces of the wrist as a result of the synovial proliferation. The proliferating synovium has enzymes, which destroy tendons, ligaments and the articular disc distal to the ulnar head. As a result of these enzymes and the pressure, communications among the radiocarpal, radioulnar and midcarpal joints develop in about 70% of patients with RA. The integrity of the distal radioulnar joint is lost; the proliferating synovium stretches the ulnar collateral ligament such that it finally either ruptures or is destroyed; and the ulnar head becomes a "floating" dorsal prominence that can be easily depressed by the examiner's fingers (Kelly et al., 1999).

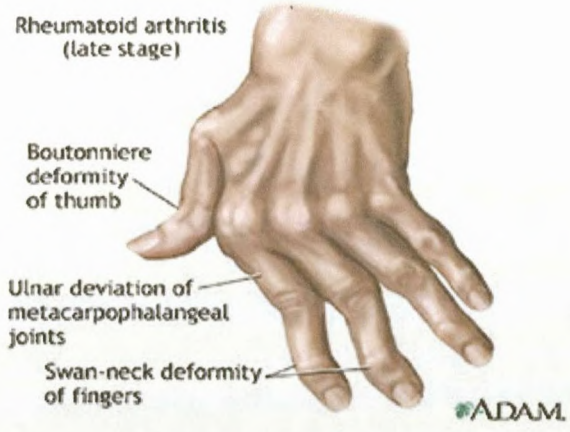


Figure 2.5: Rheumatoid Arthritis – Late Stage

Adapted from:

http://www.coretherapy.com/images/rheumatoid_arthritis_pic.jpg

Later volar subluxation (partial dislocation) of the MCP joints and ulnar deviation may develop (Mody et al., 1989; Hart, 1987). It is hypothesised that ulnar deviation of the MCP joints occurs due to a weakness of the extensor carpi ulnaris muscle, which leads to radial deviation of the

wrist due to natural rotation of the carpals (the proximal row in an ulnar direction and the distal row in a radial direction). As a result of this, ulnar deviation of the finger occurs in an attempt to keep the tendons of the phalanges in a normal line with the radius. Other potential contributing factors could also involve, for example the tendency for power grasp to pull the fingers in an ulnar direction, and inappropriate intrinsic muscle action. Ulnar deviation can occur in the absence of bony or cartilaginous erosion (Kelly et al., 1999).

Synovial protrusion cysts develop on the volar aspect of the wrist that may compress the median nerve, resulting in carpal tunnel syndrome. Common sites for bony erosion by the proliferating synovium in the wrist are the bare areas (see anatomy – 2.2) The resultant irregular bone surfaces may erode the already weakened tendons (Kelly et al., 1999).

Shortening of the intrinsic muscles exerts tension on the dorsal tendon sheath, which leads to hyperextension of the PIP joint. DIP joint flexion results from deep tendon contracture or, rarely, DIP joint involvement. Rupture of the flexor digitorum superficialis tendon could lead to the same deformity. This flexion of the DIP and MCP joints, with hyperextension of the PIP joint is known as a swan-neck deformity (Kelly et al., 1999).

Chronic inflammation of the PIP joint may cause stretching or avulsion of the extensor hood which would then pop up into flexion. The DIP joint remains in hyperextension. The result is a so-called Boutonnière deformity (Kelly et al., 1999; Hart, 1987). Boutonnière and swan-neck deformity of the fingers, Z-deformity of the thumb and arthritis mutilans are also characteristic symptoms of rheumatoid arthritis (Mody et al., 1989), but are also signs of a highly progressed pathogenesis (Haslett et al., 2001; Hart, 1987).

Resorptive arthropathy is the most serious result of RA of the hand. Severe resorption of the bone starts at the articular cartilage and then extends along the diaphysis of the affected phalanges. As a result the diaphysis appears shortened, there are excess skin folds and the phalanges can even telescope (retract) into one another (Kelly et al., 1999).

Three types of deformity of the thumb are outlined in Nalebuff's (1968) classification of thumb disease in RA.

- ☑ In type I, inflammation of the MCP joint causes the joint capsule to become stretched and a Boutonnière-like deformity develops.
- ☑ In type II the carpometacarpal joint is inflamed and this leads to volar subluxation during contracture of the adductor hallucis.
- ☑ Type III occurs with prolonged disease of both MCP joints, exaggerated adduction of the first metacarpal, flexion of the MCP joint and hyperextension of the DIP joint result from the patient's requirement to provide a pinch grip (Kelly et al., 1999; Hart, 1987).

Tenosynovitis of the flexor tendon sheath is one of the most common features of RA in the hands. It presents clinically as diffuse swelling on the volar surface of the phalanges between the joints or a palpable grating in the flexor tendon sheaths in the palm of the hand (Kelly et al., 1999).

Painful locking of a finger during flexion may occur if rheumatoid nodules develop on the tendon. If flexor tenosynovitis decreases active movement, peritendinous and pericapsular adhesions may result and limit PIP joint motion (Kelly et al., 1999).

Even in the absence of significant inflammation, the hands may be painful in a patient with RA as a result of ischaemia caused by vascular spasm from excess sympathetic tone (Kelly et al., 1999).

DIP joints have less synovial tissue than the PIP joints do and also have lower intra-articular temperatures protecting them. Thus DIP joints are less commonly involved than PIP joints in RA (Kelly et al., 1999). In addition rheumatoid arthritis also affects other joints of the body with resultant deformity and dysfunction (Bliddal et al., 1987).

The extra-articular manifestations are diverse and include conditions affecting the musculoskeletal system (e.g. tenoynovitis), lymphatic system (e.g. splenomegaly), eyes (e.g.

scleritis), cardiac system (e.g. pericarditis), pulmonary system (e.g. fibrosing alveolitis) and the neurologial system (e.g. mononeuritis multiplex). Rheumatoid arthritis also causes nodules, haematological disorders (e.g. anaemia), vasculitis, amyloidosis and systemic manifestation (e.g. fever) (Haslett et al., 2001).

It s important at this stage to note the potential differential diagnoses which need to be excluded when diagnosing with rheumatoid arthritis. The most common differential diagnoses will be discussed in no particular order.

Ankylosing spondylitis, seronegative spondylorthropathy and reactive arthritis (which are often referred to as the B27-associated diseases) need to be differentiated from RA. A problem arises in doing so in patients (especially females) who present with minimal back pain and definite involvement of the peripheral joints. RA is not as likely to be the diagnosis if the small joints are not involved, when the joint disease is asymmetric and when the lumbar spine is involved (Kelly et al., 1999).

To distinguish between RA and ***Reiter's syndrome*** one needs to examine the patient for heel pain and ocular or urethral symptoms. The presence of enthesopathy (eg sausage shape fingers indicating periaricular soft tissue inflammation); insertional tendonitis, periostitis and peri-insertional osteoporosis or erosions may point to the diagnosis of Reiter's syndrome (Kelly et al., 1999).

Differentiating between patients who have RA with ***psoriasis*** and those who have ***psoriatic arthritis*** may be difficult (Kelly et al., 1999; Hart, 1987). In psoriatic arthritis the DIP joints are classically involved and this can facilitate the diagnosis. However in some instances the joint involvement may mimic that of RA, making the diagnosis less clear (Hart, 1987).

Inflammatory bowel disease is associated with arthritis in 20% of cases. The arthritis tends to affect the peripheral joints more than the spine. It most commonly involves the ankles, knees and elbows, but the hands and wrists are also commonly involved. The symptoms of joint involvement can precede the diagnosis of the bowel disease making the correct diagnosis

of the arthritis more problematic. The attacks of joint pain tend to have a more rapid onset than in RA and usually only two or three joints are involved at any point in time (Kelly et al., 1999).

Calcium pyrophosphate dihydrate deposition disease (CPPD) is a crystal-induced synovitis that can range from an acute hot joint to a more indolent osteoarthritis. In about 5% of cases the patients have a chronic polyarthritis (sometimes referred to as Pseudo-RA), which is associated with proliferative erosions of the subchondral bone. Radiographs can aid in the diagnosis of CPPD if chondrocalcinosis is present. If this is not present then diagnosis can only be made by arthrocentesis (Kelly et al., 1999).

Systemic lupus erythematosus (SLE) is commonly associated with an inflammatory polyarthritis, which may lead to hand deformities that resemble those of RA very closely. Differentiation between the two is usually based on radiographic and laboratory findings. In SLE radiological evidence of erosions is unusual and there is a high titre of antinuclear antibodies with low levels of complement in the blood and there are also DNA antibodies present in the serum (Hart, 1987).

It is necessary to distinguish between RA and ***fibromyalgia***. In the latter there is seldom any evidence of synovitis and the pain tends to be non-articular in location. It is however also important to realise that patients with RA may develop superimposed fibromyalgia. Rheumatoid patients with fibromyalgia tend to have fewer psychological disturbances than those who have primary fibromyalgia (Kelly et al., 1999).

Glucocorticoid withdrawal syndrome may be easily confused with RA as patients experience diffuse polyarticular pain, especially in the hands. This syndrome develops if a patient, treated for non-rheumatic disorders, has their glucocorticoid dose decreased too rapidly (Kelly et al., 1999).

Chronic tophaceous gout must be excluded before a diagnosis of chronic erosive RA is made. The features that are present in both conditions are polyarthritis, symmetric distribution, spindle-shaped swelling of joints, subcutaneous nodules and the sub-acute presentation of

attacks. Radiographically, the small osseous tophi in gout may closely resemble the sub-cortical erosions of RA. However if there are large asymmetric erosions with ballooning of the cortex visible on X-rays the diagnosis is more likely to be gout. Laboratory tests may also be misleading as Rh factor can be positive in as many as 30% of patients with tophaceous gout who have no clinical or radiographic features of RA (Kelly et al., 1999).

Infectious arthritis must be differentiated from rheumatoid arthritis although the first may be superimposed on the latter. Infections with organisms such as polio, rubella or Epstein –Barr virus, to name but a few, may present as arthritis, with many characteristics similar to RA (Kelly et al., 1999). Synovitis is not as severe and joint damage with radiologically evident destruction is less common. There may also be other systemic manifestations of the infection such as rashes (Hart, 1987). Laboratory tests specific to each organism will need to be conducted in order to make a definitive diagnosis (Kelly et al., 1999).

The differentiation between RA and ***Lyme disease*** can be problematic as the latters' clinical presentation closely resembles that of RA in both adults and children. It has an intermittent course involving the development of chronic synovitis. The proliferative synovium that can develop in Lyme disease is not different from that of RA (Kelly et al., 1999).

The possible existence of ***malignancy*** must also be excluded in patients suspected of having RA. Malignant involvement of the synovium is usually monoarticular in nature. However, ***non-Hodgkins lymphoma*** may present as a seronegative polyarthritis without lymphadenopathy or hepatomegally. In children, ***acute lymphocytic leukaemia*** can also manifest as polyarticular arthritis. A detailed history, thorough physical examination, and laboratory tests (if indicated) will be necessary to assess the possibility of malignancy as a differential diagnosis (Kelly et al., 1999).

Osteoarthritis (OA) begins as degeneration of the articular cartilage and RA begins as an inflammation in the synovium. However, in the end stages of OA and RA the joints appear the same. To distinguish between the two it is therefore the early history and functional abnormalities of the disease that are important for the physician to note. RA can start in

individuals as young as 20 with no evidence of trauma to the joint and they usually present with morning stiffness that eases during the day. The most commonly involved joints are the wrists, MCP, PIP joints; these have surrounding soft tissue swelling and are warm. The DIP joints are almost never affected. Radiographially there is evidence of periarticular osteopenia and marginal erosions. Laboratory tests reveal increased ESR, Rh factor (in 80% of cases), anaemia and leucocytosis. In contrast the incidence of OA increases with increased age and patients usually have a history of trauma or congenital abnormalities (e.g. a shallow acetabulum). They typically present with pain that increases during the course of the day. The most commonly involved joints are the DIP joints (Heberden's nodes) and weight-bearing joints (hips and knees), and these develop bony osteophytes but there is minimal soft tissue swelling. Radiographs show evidence of subchondral sclerosis and osteophytes and laboratory test are normal (Kelly et al., 1999).

2.6) Current Treatments:

The treatment of rheumatoid arthritis is aimed at the relief of symptoms, suppressing the progression of the disease and the conservation and restoration of function in the affected joints (Haslett et al., 2001). This is addressed through the treatment of the patient by drugs, rest, physical therapy and surgery combined with modification of the environment (e.g. aids, appliances, etc).

A wide range of drugs are used in an attempt to manage rheumatoid arthritis effectively. ***Nonsteroidal anti-inflammatoy drugs*** (NSAIDS) may provide important symptomatic relief but they do not appear to alter the diseases' long-term course (Boers et al., 1999; Hart, 1987). ***Salicyclates,*** a class of NSAID, are relatively inexpensive drugs with analgesic and anti-inflammatory effects that are commonly used to treat rheumatoid arthritis (Boers et al., 1999). These drugs however have major side effects, which include:

- ☑ Ototoxicity,
- ☑ Hypersensitivity reactions (e.g. asthma or urticaria),
- ☑ Cutaneous reactions (e.g. pruritis and non-specific rashes),

- ☑ Hepatic effects (most often mild, asymptomatic elevations of one or more hepatic enzyme),
- ☑ Central nervous system (CNS) effects (uncommon with most NSAIDS but common with indomethacin),
- ☑ Renal effects (hyperkalaemia and renal failure are of the most concern),
- ☑ Gastrointestinal (GI) effects (e.g. bleeding, gastric erosions and ulceration) and
- ☑ Hematologic effects such as aplastic anaemia, agranulocytosis and thrombocytopenia (Kelly et al., 1999; Hardin et al., 1992).

Many rheumatologists believe that salicyclates have been rendered outmoded by newer nonsalicyclate NSAIDS. However in most instances of classical inflammation, the newer agents have no discernable advantages in terms of efficacy. Many of the side effects of NSAIDS can be minimised by the choice of an appropriate salicyclate. In terms of convenience, efficacy, toxicity, and expense, salicyclates appear to be the first choice in most clinical situations where NSAIDS are indicated. NSAIDS, however, seldom completely relieve all the symptoms of inflammation (e.g. swelling and tenderness) (Hardin et al., 1992).

Gold compounds are usually given in addition to salicyclates and other NSAIDS if these are in themselves insufficient. In some instances gold may result in clinical remission and a decrease in the formation of bony erosions (Boers et al., 1999). Gold can be administered either parenterally or orally. Parenteral gold can cause vasomotor reactions (flushing, headache, syncope / near syncope, nausea and sweating), arthralgias / myalgias (arthritis flare-up), mucocutaneous reactions (e.g. stomatitis and alopecia), renal complications (e.g. proteinuria and nephritic syndrome) and hematopoietic complications such as eosinophilia and aplastic anaemia (Kelly et al., 1999; Hardin et al., 1992).

The toxicity of oral gold is significantly less than that of parenteral gold. Approximately 50% of patients will experience loose stools or diarrhoea, abdominal discomfort and nausea. Rashes, with and without pruritis, occur in about 25% of patients taking oral gold, and 13% develop stomatitis, with proteinuria, thrombocytopenia and leukopenia only reported in 1% of patients.

The cost of gold compounds (oral and parenteral) is also high in comparison to other antirheumatic drugs (Kelly et al., 1999; Hardin et al., 1992).

Oral ***penicilamine*** may have an effect similar to that of gold and is sometimes used if gold fails or produces toxicity in patients with active RA (Boers et al., 1999). Side effects of oral penicilamine include: hematologic toxicity (e.g. thrombcytopena), nephropathy, dermatologic reactions (e.g. pruritis), GI symptoms (e.g. anorexia and nausea), pulmonary complications (e.g. a Goodpasture-like syndrome), neuromuscular disorders (e.g. myasthenia gravis) and autoimmune syndromes (e.g. Wilson's disease). The side effects and loss of efficacy of the drug often lead to a high number of withdrawals from the drug (Kelly et al., 1999; Hardin et al., 1992).

Sulphasalazine is now increasingly used in the treatment of rheumatoid arthritis and the effects are seen within 3 months of initiating treatment (Boers et al., 1999). It is approximately as effective as more traditional antirheumatic drugs (e.g. gold and penicilamine) but acts faster and causes fewer side effects. The most common adverse effects include: gastrointestinal complications (e.g. nausea and vomiting) and CNS symptoms (e.g. dizziness). Less common adverse effects involve the skin (e.g. rash), liver (e.g. marginal enzyme elevations) and blood (e.g. hemolysis) (Kelly et al., 1999).

In addition ***Methotrexate*** has become an established treatment for rheumatoid arthritis. It is administered as a low-dose on a weekly basis as more frequent use is associated with a greater incidence of acute and / or chronic toxicity. Adverse reactions due to low-dose methotrexate are relatively common, however severe toxicity appears to be rare (Kelly et al., 1999). The common, and usually not serious, side effects include nausea and vomiting, abdominal discomfort, diarrhoea, pruritis, stomatitis, abnormal liver tests, macrocytosis, alopecia, headache and memory impairment. The common, and potentially serious complications are thrombocytopenia, leukopenia and pancytopenia. Uncommon, but potentially lethal side effects are pulmonary infiltrates with hypoxemia, hepatic cirrhosis and acute liver failure (Hardin et al., 1992).

Corticosteroids are, however, the most effective short-term anti-inflammatory drugs used in RA, however the benefit seems to decrease with time (Boers, et al. 1999). From the beginning, during initial trials of cortisone in patients with RA, it has been evident that the dramatic anti-inflammatory effects of glucocorticoids are frequently accompanied by the development of iatrogenic Cushing's syndrome. The features of this syndrome include: benign intracranial hypertension, glaucoma, centralised obesity, pancreatitis, avascular necrosis of bone, hirsuitism, plethora, and striae to name but a few. Cushing's syndrome is a serious disorder and the 5-year mortality rate was over 50% in a series of studies that were conducted when corticosteroid and ACTH therapy were first introduced. Side effects are numerous and diverse, affecting most bodily systems including the eyes (e.g. exopthalmus), cardiovascular system (e.g. congestive cardiac failure), gastrointestinal system (e.g. peptic ulcers), neurological system (e.g. convulsions), musculoskeletal system (e.g. osteoporosis), endocrine system (e.g. diabetic ketoacidosis) and any more (Boers et al., 1999; Haslett et al., 2001; Kelly et al., 1999; Hardin et al., 1992).

Due to the myriad of potential side effects of traditional medical treatment and the fact that despite these treatments many patients still suffer from the disabling effects of RA, conservative treatment needs to be considered as well. Joint protection (multifaceted approach to altering the way in which functional daily activities are performed in an attempt to protect the involved joints) aims to reduce pain, inflammation and both internal and external joint stresses. As a result it helps preserve the integrity of joint structures and reduces the risk of deformities (Turner et al., 1998). Joint splinting helps to reduce local inflammation and may relieve local symptoms. These joint splints also theoretically help to reduce stress on the joint capsule and allow muscles to relax (Turner et al., 1998). Passive exercise within the limits of pain can be utilised during the inflammatory stage to help prevent contracture formation. As the inflammation recedes, active exercise can help to restore muscle mass and maintain normal joint range of motion. In order to address established joint contractures the individual may need to do extensive exercise and undergo serial splinting or orthopaedic interventions (Haslett et al., 2001). It must however be noted that these interventions are more rehabilitative in nature than restorative in nature.

It has therefore been suggested that the physiological effects of LLLT, which are biostimulation, improved metabolism, increased cell metabolism, improved blood circulation, vasodilatation, analgesic effect, anti-inflammatory and anti-edematous effects; may be more effective in treating the RA symptoms from a restorative perspective (Liggins, 2002).

The basis for these effects is the fact that diseased or damaged tissues releases superoxide radicals, an inflammatory mediator, which combines with arachidonic acid to form prostaglandin E2 (PgE2). This converts adenotriphosphate (ATP) into cyclic adenomonophosphate (cyclic AMP) that in turn results in an increased sensitivity of the nociceptors resulting in increased levels of pain. Irradiation with low level laser results in the release of superoxide dismutase (SOD) that scavenges the superoxide radicals which decreases the amount of PgE2 produced. Low-level laser also causes a photochemical reaction, which converts prostaglandins to prostacyclin endoperoxide with a resultant decrease in the sensitivity of the nociceptors, thus further reducing pain (Liggins, 2002). Furthermore LLLT has been shown in some studies to result in a decrease in the level of perceived pain (Asada et al., 1991; Boers et al., 1999; Heussler et al., 1993; Johannsen et al., 1994; Walker et al., 1987). The reduction in PG-E2 (which promotes inflammation by potentiating the effects of other inflammatory mediators) will also result in a decrease in inflammation in the joint. Thus there will also be a decrease in the duration of morning stiffness, which occurs as a result of the accumulation of the inflammatory substances in the joint (Kelly et al., 1999).

The various settings that can be altered according to the practioner's personal preferences when administering low-level laser therapy (e.g. frequency, pulsed/continuous, joules, etc) have lead to a fragmented picture of the true efficacy of low-level laser therapy in the treatment of RA. The final portion of this chapter will therefore discuss previous studies that have been conducted and will attempt to indicate how these studies could have been improved upon.

2.7) Previous studies

The double blind placebo controlled clinical trial of 18 patients conducted by Bliddal et al., (1987) administered LLLT to the patient's one hand using a type C biotronic laser giving

continuous He-Ne (Helium-neon) laser irradiation at 633 nm and 10 mW. The patient's contralateral hand was used as the placebo and was treated using an apparatus containing a red 12V, 10 W bulb and a reflecting mirror. The treatments were administered on three alternate days a week for three consecutive weeks followed by a four-week observation period. They found that although there was a shorter duration of morning stiffness during treatment, no significant effects were recorded. The joint ability score (JAS) showed improvement in both the laser- and placebo- treated hands but this difference did not reach statistical significance. The readings from the visual analogue scale (VAS) showed improvement during treatment most noticeably in the laser-treated side. No changes in laboratory tests (sedimentation rate, hemoglobin, leukocyte and platelet counts) were noted, and there were no differences seen in these parameters between responders and non-responders to treatment (Bliddal et al., 1987).

The double blind placebo controlled clinical trial on 72 patients conducted by Walker et al., (1987) using a low-power helium-neon laser giving continuous laser irradiation at 632,5 nm; 1mW and 20Hz supports the findings of Bliddal et al., (1987). However in this case each patient was treated three times per week for ten weeks. The skin overlying the radial, median and saphenous nerves was irradiated bilaterally for 20 seconds per site. This was followed by irradiation of the skin overlying the painful joints. The total treatment time for each patient was four minutes for the first four weeks and was increased to six minutes for weeks five to seventh and then further increased to eight minutes for the eighth to tenth weeks. They found a significant improvement in the visual analogue scale readings in the treatment group as compared to the placebo group (Walker et al., 1987).

It must be noted from the above studies (Bliddal et al., 1987; and Walker et al., 1987) that although there was improvement noted in the patients, there was a lack of consistency in the clinical findings that suggests that these two studies have a methodological flaw, for example it would seem logical that with decreased morning stiffness, that there should be a significant change in the JAS (joint ability score) score as well. Thus further studies with different units where utilized in order to test the same hypotheses.

In contrast to the above, in a clinical trial conducted on 35 patients by Palmagren et al., (1989) a Biotherapy 3 laser (gallium-aluminium-arsenate semiconductor laser diode) was used to administer continuous irradiation at 820nm and 15 mW. Eight finger joints, [2nd to 5th metacarpophalangeal (MCP) and proximal interphalangeal joints (PIP)] of the most affected hands were treated three times per week for four weeks. They noted a clinical improvement in the patients as well as biochemical evidence of reduced activity in the disease (Palmagren et al., 1989), which suggests that there is clinical outcomes congruence.

Thereafter Heussler et al., (1993) and Hall et al., (1994) also used GA-Al-As lasers giving pulsed irradiation at 820nm and 5000Hz but they used a setting of 50mW. They both conducted their studies as randomized double-blind placebo-controlled clinical trials. However, where Heussler et al., (1993) used the patient's contralateral hand as the placebo, Hall et al., (1994) had separate treatment and placebo groups. In the study by Heussler et al., (1993), 25 patients had their MCP and PIP joints of one hand treated three times per week for four weeks. The patient's contralateral hand that was used as the placebo was treated for the same period of time using a sham laser. They reported that 72% of the patients experienced pain relief equal for both hands. There were no significant changes in other clinical, functional, scintigraphic or lab features (Heussler et al., 1993).

Hall et al., (1994) conducted their clinical trial on 40 patients. The hand that the patient considered to be the most affected was treated, which in most cases was the dominant hand. They found no difference in the objective and subjective findings between the laser and placebo groups after 12 treatments and at the follow-ups over a three-month period. They noted that there was no improvement in any of the objective or subjective measurements in the treated or placebo group. The patients' perceptions, recorded at each assessment, were that they did not feel that the treatment had been effective in terms of reducing the pain or swelling and that there was no increase in their activities of daily living (Hall et al., 1994).

This tends to indicate that LLLT has very little efficacy in the face of placebo, yet the previous studies seem to indicate either clinical or biochemical changes over time even in the face of methodological flaws within the studies. In terms of the Hall et al., (1994) study which

addressed the issue of placebo controls in patients that were not actively treated, no improvement was noted in the patients, this would however be linked to the changes affected at the level of dose and time application of the LLLT.

Concurrently with the Hall et al., (1994) study, a double-blind placebo-controlled clinical trial was conducted on 22 patients by Johannsen et al., (1994) using a Ga-Al-As laser to administer continuous irradiation at 830nm and 21 mW. The two most painful joints on the most affected hand were chosen for treatment. Treatments were offered three times a week for a month. They found laser to have an effect on the pain score but when they attempted to correct for disease variance (this was done by subtracting the improvement seen in the patients contralateral hand), the effect disappeared (Johannsen et al., 1994). This seems to support the findings of the studies prior to 1994 in that improvement was noted. The correction for disease variance by using the contralateral hand as the measure of the disease however assumed that the treatment effect of laser cannot be systemic, thereby nullifying results that could have shown improvement bilaterally (and not nothing / insignificant as noted by Johannsen et al., (1994)).

Lee et al., (2003) conducted a study on the effect of low-level laser in the management of common musculoskeletal pain syndromes. Forty patients with pain of musculoskeletal origin were evaluated. Among their main complaints was wrist pain, arm pain and tingling or numbness of the hands. A low-level infrared laser light emitting 100 – 300mW and 830nm was applied to the site of pain. The following results were obtained: six patients had complete relief, 34 patients had decreased pain and none reported a worsening of their symptoms or no pain relief (Lee et al., 2003). This indicates that there is a at least a 15% chance of improving the clinical presentation of the patient to the point of no clinical symptoms and an 85% chance of obtaining better clinical outcomes according to Lee et al., (2003).

Nevertheless as a result of these conflicting studies, Brosseau et al., (2002) conducted a Cochrane review on the efficacy of LLLT in treating rheumatoid arthritis. They selected only randomized controlled trials of LLLT for the treatment of individuals with a clinical diagnosis of rheumatoid arthritis. The literature review identified 8 trials that met the inclusion criteria. Five

of these were randomized controlled trials of laser versus a placebo with a separate control group (Walker et al., 1987; Palmagren et al., 1989; Goats et al., 1996; Hall et al., 1994; Johannsen et al., 1994). Three of the trials used the patients' contralateral hand as the control (Goldman et al., 1980; Bliddal et al., 1987; Heussler et al., 1993).

Brosseau et al., (2002) noted that LLLT :

- ☑ decreased pain by 70% relative to placebo,
- ☑ decreased the duration of morning stiffness by 27,5 minutes and
- ☑ increased tip to palm flexibility by 1,3cm.

There was however no statistical improvement in localized swelling, muscle strength, functional status, joint tenderness or global assessments. Furthermore there were no significant differences in LLLT dosage, wavelength, site of application or treatment length between the different subgroups.

However in studies in which the contra-lateral hand was used as the control group, there was no difference between the two groups but both hands improved in terms of pain relief and disease activity, supporting the assertion that the LLLT has systemic effects. Thus the use of the patients' contralateral hand as the placebo by Bliddal et al., (1987); Heussler et al. (1993); and Johannsen et al., (1994), disregards the possible systemic effects of laser that could have had an analgesic effect on the contralateral hand (Baxter, 1994). Therefore when they attempted to correct for disease variance (which was done by subtracting the improvement seen in the patient's contralateral hand) they may have disregarded the true effectiveness of the treatment.

2.8) Summary:

In many of the studies it is not clear whether or not long-term follow-ups were done after the low-level laser therapy. Baxter (1994) has highlighted the importance of assessing the long-term effects of low-level therapy, as there is a paucity of this information in the currently available literature (Boers et al., 1999). In addition the lack of a standardized approach to the selection of laser parameters has made it difficult to compare studies and may well account for

the widely differing findings that have emerged from past research. This discrepancy has led to an uncertainty in the literature about the true efficacy of this form of treatment (Boers et al., 1999).

Thus this research was aimed at overcoming these potential limitations by having had separate treatment and placebo groups, having utilized laser parameters that were selected based on the parameters used in previous successful research (within the limitations of the low-level laser unit available) and by having incorporated a one-month follow-up visit in the research design.

CHAPTER THREE

MATERIALS AND METHODS

3.1) Study Design and Protocol:

This study is a quantitative pragmatic controlled clinical trial.

3.1.1) Advertising

It included 24 participants with rheumatoid arthritis affecting their hands that presented to the Durban Institute of Technology (DIT) Chiropractic Day Clinic. Posters advertising the study were displayed at shopping centres, health shops, libraries, factories and chemists. Pamphlets were distributed into post boxes and P.O Boxes and matrons at local old age homes were approached about potential patients. Individuals attending the Nkosi Albert Luthuli Arthritis Clinic were informed about the study and were given pamphlets with information pertaining to it. All of those who responded were interviewed telephonically, or personally by the researcher, as they presented to the clinic, to determine whether they complied with the selection criteria.

3.1.2) Sampling

3.1.2.1) Method

The patients voluntarily offered to participate in the study as the result of advertisements of pamphlets they had seen (self selection).
If the patients were found to fit into the study (having taken the inclusion and exclusion criteria into account), then they were included in the study (convenience sampling).

3.1.2.2) Allocation

Patients were allocated to different categories (groups) based on the outcome of the DASH questionnaire and their primary medication. For the purpose of this study a score on the DASH questionnaire of 0-33 constituted a mild disability, 34-66 a moderate disability and 67-100 a severe disability. An example of this would be that the first patient who presents with mild symptoms and is on a particular medication will be placed into group A the second patient who falls into the same category will be placed into group B.

3.1.2.3) Size

At the outset a sample of 40 patients (20 in the treatment group and 20 in the placebo group) was sought. However due to the following problems a final sample of 24 patients (16 in the treatment group and 8 in the placebo group) was used:

Methodological parameters:

- Many of the patients that presented at the clinic had other forms of arthritis (e.g. osteoarthritis) instead of RA or they had other forms of arthritis (e.g. psoriatic arthritis) in addition to RA. In both cases the patients had to be excluded from the study.

- Two patients had to be excluded due to a misdiagnosis of RA by their rheumatologists, who in fact had systemic lupus erythematosus, which was only diagnosed on a subsequent visit.
- The long duration of the protocol made it difficult for patients who did not have their own transport or who did not live close to the clinic to complete the research protocol. This was especially problematic for patients recruited at Nkosi Albert Luthuli hospital as many of them lived in areas outside of Durban.

Patient parameters:

- Some patients had to drop out due to unavoidable circumstances (e.g. sent on a three week course, in another province, by the government).
- There was no location where there was a high density of RA patients (who were not being hospitalized due to an acute flare-up in their RA) at which the research could be conducted.
- Extensive advertising and other attempts at recruiting patients did not yield many patients who met all the criteria for inclusion in the study.

3.1.3) Standard of Acceptance:

- **Telephonic Interview as a Screening Process:**

The following information was obtained either telephonically from interested participants, or directly from those who presented to the clinic.

- Participants had to have had their rheumatoid arthritis diagnosed. If this was not the case, they were required to have blood tests completed prior to inclusion into the study. These tests included the rheumatoid factor and eosinophil sedimentation rate, both of which had to both be high in order for the person to be included in the study (Boers et al., 1999; Hart, 1987; Haslett et al., 1994; Kelly et al., 1993).

- Participants could not have had any change in their dosage of NSAIDS (in the previous month) or disease-modifying anti-rheumatic drugs (in the previous three months) (Hall et al., 1994).
- Participants had to be between the ages of 20 and 75 years (see inclusion criteria for explanation).
- Participants could not have any other arthritic disease (e.g. psoriatic arthritis, Reiter's syndrome, etc.), cancer or serious infection of their hands (Kelly et al., 1993).
- Participants could not be pregnant (Baxter et al., 1994; Heussler et al., 1993; Johannsen et al., 1994; Kahn, 1994; Kitchen et al., 1996; Liggins, 2002).

The potential candidates who met the requirements of the telephonic or personal interview were then scheduled for an initial consultation during which they received a patient information letter (Appendix A), informing them of the nature of the research, the selection criteria, and what would be required of them, should they be accepted into the study.

The candidates then underwent a case history (Appendix C), a physical examination (Appendix D), and a hand and wrist regional examination (Appendix E). They were subsequently required to sign an informed consent form (Appendix B) if they were deemed to fit the criteria of the study and included.

These assessments, along with the inclusion and exclusion criteria discussed below, were used to select 24 candidates for participation in the study.

3.1.4) Inclusion Criteria:

In order to be accepted, the applicants had to fulfil the following criteria (Asada et al., 1991; Goats et al., 1996; Shaik, 2003; Palmagren et al., 1989).

- The patient had to meet the American Rheumatism Association's diagnostic criteria for rheumatoid arthritis (Boers et al., 1999) (Appendix L):

  Any four of the following must be present to classify patients as having rheumatoid arthritis.

  - Morning stiffness for > 1 hour *
  - Arthritis of three or more joint areas *
  - Arthritis of hand joints (wrist, metacarpophalangeal or proximal interphalangeal joints) *
  - Symmetric arthritis *
  - Rheumatoid arthritis
  - Serum rheumatoid factor
  - Radiographic changes (hand x-ray changes typical of rheumatoid arthritis had to include erosions or unequivocal bony decalcification)

  (* Must have been present for 6 weeks or longer)

- The patient had to have a functional capacity of II or III according to the Classification of Functional Status in Rheumatoid Arthritis. (Appendix M).
  - Class I: Completely able to perform usual activities of daily living (self-care, vocational and avocational[1]).
  - Class II: Able to perform usual self-care[2] and vocational activities, but limited in avocational activities.

[1] Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex – specific.

[2] Usual self-care activities include dressing, feeding, bathing, grooming, and toileting.

- Class III: Able to perform usual self-care activities, but limited in vocational and avocational activities.
- Class IV: Limited in ability to perform usual self-care, vocational, and avocational activities.

❖ The patient had to be between the ages of 20 and 75 years (Walker et al., 1987). Although rheumatoid arthritis is noted internationally as occurring between 20 and 60 years of age (Haslett et al., 2001) the age group range was extended to 75 years for this study in order to take cognisance of the fact that the situation in South Africa may be different.

3.1.5) Exclusion Criteria:

Applicants were excluded from the study for the following reasons.

1) Any change in the treatment of their rheumatoid arthritis (e.g. NSAIDS and DMARDS) during the course of the study (Hall et al., 1994; Johannsen et al., 1994).
2) Changes in their dosage of NSAIDS (non-steroidal anti-inflammatory drugs) in the previous month or DMARDS (disease modifying anti-rheumatic drugs) in the previous three months (Hall et al., 1994; Johannsen et al., 1994).
3) An acute inflammatory episode during the treatment period (Heussler et al., 1993).
4) Pregnancy (Baxter et al., 1994; Heussler et al., 1993; Johannsen et al., 1994; Kahn, 1994; Kitchen et al., 1996; Liggins, 2002) as this has an ameliorating effect on RA in more than 75% of pregnant patients with RA (Kelly et al., 1993).
5) Other inflammatory arthritic diseases (e.g. psoriatic arthritis, Reiter's syndrome, etc.) as some of their presenting clinical features may be

attributed to RA and thus cause irregularities in the results (Johannsen et al., 1994).

6) The standard contraindications for laser therapy: (Baxter, 1994; Kahn, 1994; Kitchen et al., 1996; Liggins, 2002)
    - Active or suspected carcinoma
    - Areas of haemorrhage
    - Area of infected tissue
7) Recent major trauma or surgery to the hand.

3.2 Intervention:

3.2.1) Treatment Procedure and Frequency

As indicated previously, 24 patients were selected as participants during the initial consultation, at which the case history, physical and regional examinations where completed, in order to ensure compliance with the inclusion and exclusion criteria. The participants were then asked to record the duration of their morning stiffness over the course of a week (Monday to Monday).

They were asked to come in for their first treatment on the following Monday at which stage they were assessed and each patient was then assigned to a group base on his or her DASH score.

Participants were assigned to different categories based on the outcome of the DASH questionnaire and their primary medication. For the purpose of this study a score on the DASH questionnaire of 0-33 constituted a mild disability, 34-66 a moderate disability and 67-100 a severe disability. An example of this would be that the first participant who presents with mild symptoms and is on a particular medication will be placed into group A the second participant who falls into the same category will be placed into group B.

All participants then received three treatments a week (e.g. on a Monday, a Wednesday and a Friday) for three weeks. They were reassessed before the seventh treatment, again during the week following their final treatment and finally during the fourth week after their final treatment (a one month follow up).

WEEK PLANNER

WEEK	MON	TUES	WED	THURS	FRI
1	Assess	Patient	During	This	Week.
2	Start morning stiff ness recordings.				
3	Reading 1 Treatment 1		Treatment 2		Treatment 3
4	Treatment 4		Treatment 5		Treatment 6
5	Reading 2 Treatment 7		Treatment 8		Treatment 9
6	Reading 3				
7					
8					
9	Start morning stiffness recordings for follow up.				
10	Reading 4 (Follow up)				

Group A:

The laser was applied in the manner recommended by Baxter (1994) and Kahn (1994). Group A received LLLT of the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints of the more severely affected hand. The open joint technique of application was utilised with the laser being applied in direct contact with the anterior, posterior, medial and lateral surfaces of the joints. The laser beam was directed at 90° (cosine law and law of reflection) to the surface so as to enhance penetration of the laser beam (Fischer, 1987).

For the purpose of this study the following parameters were used, based on an average from a literature review, but within the range that the available laser unit permitted.

1) Power output: 20mW.
2) Wavelength: 675nm.
3) Pulse repetition rate: 5000Hz (Hall et al., 1994; Heussler et al., 1993).
4) Time per spot: 30 seconds (Heussler et al., 1993; Johannsen et al., 1994; Liggins, 2002).
5) Joints treated: Proximal interphalangeal (PIP) joints and metacarpophalangeal (MCP) joints (Hall et al. 1994; Liggins, 2002, Palmagren et al., 1989) of all five digits of the most severely affected hand.
6) Laser technique: Open joint technique – in contact with skin (Baxter, 1994; Boers et al., 1999; Hall et al., 1994; Johannsen et al., 1994; Kahn, 1994; Liggins, 2002).
7) Treatment frequency: nine treatments over three consecutive weeks (three treatments per week) (Jensen et al., 1987).

Group B

The patients in group A received LLLT and the patients in group B were treated with a laser that was not turned on. Group B's treatment was applied to the same joints, using the same technique and for the same number of treatments as the treatment group.

Group B was included as a control group to help determine whether the improvement seen during the treatment period in Group A was likely to be as a result of the LLLT, or whether it was merely a manifestation of the natural fluctuating course of RA. If similar improvements were not seen in the treatment and the control group, then one could reasonably assume that any changes seen in the participants' hand symptoms could be as a result of the LLLT.

3.3) Materials and Measurements:

3.3.1) Subjective Measurements:

These consisted of the Numerical Rating Scale-101 (NRS-101), Disability of the Arm, Shoulder and Hand (DASH) Questionnaire and the duration of morning stiffness.

3.3.1.1) NRS-101: (Appendix H)

The participants' perception of their pain intensity level was recorded on a numerical scale from 0 to 100, with 0 being no pain and 100 being the worst pain. The patient indicated by means of a percentage on a 10cm line, when the pain was at its worst and again on another 10cm line when the pain was at its least.

These two values were then added together and divided by two in order to give an average of the values. If the average increased over time it meant that the perceived pain was getting more severe, and if the average decreased it meant that the perceived pain was getting less severe.

Jensen et al., (1987) stated that the NRS-101 questionnaire is regarded as a superior measuring instrument, being extremely easy to administer and score. It can be done in written or verbal form, and as a result of its simplicity, there are very low tendencies for incorrect responses from participants.

3.3.1.2) DASH Questionnaire: (Appendix I)

Gummesson et al., (2005) stated that the DASH questionnaire could detect and differentiate small and large changes in disability over time in patients with upper

extremity musculoskeletal disorders. Due to the clarity of the response choices and the easy-to-follow nature of the questionnaire, there are very low tendencies for incorrect responses from participants.

A study conducted by Beaton et al., (2001) found that the DASH questionnaire was reliable and exhibited test-retest responsiveness. The DASH was also found to have validiy and responsiveness for proximal (e.g. shoulder) and distal (e.g. hand) disorders, thus confirming its usefulness in assessing the whole upper extremity (Beaton et al., 2001).

Thus the participants' perception of their daily functional ability was assessed by having had them complete a questionnaire that focused on their ability to perform certain daily activities that are influenced by upper limb functioning.

They were asked to complete the main part of a 30-item disability / symptom scale concerning their health status during the previous week. The items asked about the degree of difficulty in performing different physical activities because of the arm, shoulder or hand problem (21 items), the severity of each of the symptoms of pain, activity-related pain, tingling, weakness and stiffness (five items), as well as the problems impact on social activities, work, sleep and self-image (four items). Each item had five response options.

The scores for all items were added together, 30 was then subtracted from the total and the resultant number was then divided by 1.2. This yielded a score ranging from 0 (no disability) to 100 (most severe disability). The score for the disability / symptom scale is called the DASH score. An increase in the DASH score would have indicated that the patient's ability to perform functional daily activities had decreased (i.e. increased disability). A decrease in the patient's DASH score would have indicated that their ability to perform functional daily activities had increased (i.e. decreased disability).

3.3.1.3) Duration of Morning Stiffness (Appendix J):

Prolonged morning stiffness, usually greater than one hour in duration, is a clinical feature of RA, and the stiffness decreases slowly during the day until a plateau is reached (Boers et al., 1999; Hart, 1987; Kelly et al., 1993; Kumar et al., 2001; Yochum et al., 1996).

The participants were asked to record on a daily basis the amount of time taken for their morning stiffness to reach that plateau, the values were recorded in a table format. An average for the week was calculated by adding all the values for one week (Monday to Monday) and then dividing by seven to give the average duration of morning stiffness experienced per day.

A decrease in the average indicated a decrease in the duration of morning stiffness experienced by the patient, whilst an increased average indicated that the patient experienced an increased duration of morning stiffness.

3.3.2) Objective Measurement:

This consisted of algometer readings.

3.3.2.1) Algometer (Appendix K):

An algometer, also known as a pressure or force gauge, is used for the assessment of local pain sensitivity. It has been used extensively to evaluate pain in conditions ranging from abdominal pain to fibrositis, and even in psychological research (Fischer, 1987).

The algometer is a force gauge (calibrated in lb/cm^2) that is fitted with a metal disc having a surface area of $1cm^2$. Pressure is applied, via the metal disc, to a

defined surface on the body. The algometer consists of a body attached to a metal rod with a male tread on the end, onto which the metal disc is attached. When pressure is exerted on the rod, the indicator moves in a clockwise direction around the dial on he body. The zeroing button is pressed after each measurement, and this returns the indicator to zero. The achieved force value is held until the zeroing button is pressed (maximum hold function), this allows a reading to be taken even once the algometer has been removed from the body (Fischer, 1987).

The participants were first educated on how the gauge operated before measurements were taken. They were requested to indicate which of their MCP and PIP joints (on their most severely affected hand) was the most problematic and which was the least. They were then told that the algometer would be placed on the palmar aspect of these joints and pressure would be applied. The pressure would be slowly increased until the pressure sensation turned to pain (pain threshold point) at which stage the patient must inform the researcher that such a change has taken place (Fischer, 1987).

These two readings (from the most and least problematic joints) were then added together and divided by two in order give their average.

The less tender the area under investigation is, the higher the algometer reading is, and a lower reading indicates a greater tenderness (Fischer, 1987).

Therefore an increase in the average algometer reading indicated that the patients' joints were less tender to pressure. A decreased average algometer reading indicated that the patients' joints were more tender to pressure.

3.4 Statistical analysis

Data analysis was done in SAS version 9.1 (SAS Institute Inc., Cary, NC).

The demographic data are summarised at baseline for the two groups. Baseline comparisons between the categorical baseline variables and the group to which the participant was assigned were done using Fisher's exact test. Continuous normally distributed baseline data were compared using the two sample t-test.

Since the same measurements were repeated for each subject at four separate times, a repeated measures analysis of variance (ANOVA) was used to analyse the treatment effect over time. The repeated effects were the four readings of the same variable and the covariate is the treatment assignment. A p-value was then given for the time effect (whether there was a change in the readings over time) and for the treatment effect (whether there was a difference between the readings for the treatment and placebo groups). A visit by treatment interaction effect was also investigated.

In addition to these a paired t-test was done on the change from baseline to endpoint to determine whether there was any treatment difference between the two groups.

A graph was drawn of each variable, giving the mean and median values at each time point in both the treatment and placebo groups.

CHAPTER FOUR

RESULTS

4.1. Introduction:

In this chapter a basic explanation of new terms that are used therein is given and the demographic data of the patients involved in the study are looked at. The results of the research and the statistical analysis of these results are also presented.

4.1.1) Data

4.1.1.1) Primary Data

The following measurements were obtained:

a) Subjective Measures:

- NRS 101 – which is expressed as a score out of 100.
- DASH Questionnaire – Which is expressed as a score out of 100.
- Morning Stiffness – Which is expressed in minutes.

b) Objective Measure:

- Algometer Readings – which are expressed as a numerical value measured in lb/cm^2.

4.1.1.2) Secondary Data

Secondary data were obtained from books, journals, lecture notes and the internet.

4.1.2) Key Terms

- **p-value** – This value assists the researcher in deciding whether the changes seen in the mean scores of the treatment group are due to the treatment rather than chance. The usual convention is that the researcher must be 95% certain that the improvement in post-treatment scores was caused by the treatment. This probability level is expressed as $p \leq 0.05$ (Bailey, 1997).

- **N** - sample size
- **Mean** – This is essentially the average. It is found by taking the sum of the observations and dividing by their number (Bland, 1996).
- **Median** – This is the central value of the distribution, and thus half the readings are less than or equal to it and the other half are greater than or equal to it (Bland, 1996).
- **Standard deviation (Std dev)** – This reflects the variability in the data. It looks at the variance of the readings from the mean. If the readings are widely scattered then the standard deviation would be large, whereas if the readings are narrowly dispersed the standard deviation would be small (Campbell, et al. 1999).
- **Null hypothesis** – when carrying out a significance test (which asks whether the difference observed was small enough to have occurred by chance) we suppose that in the given population, there is no difference between the treatment and the placebo. The hypothesis of "no difference" or "no effect" in the population is called the null hypothesis (Bland, 1996).
- **Alternative hypothesis** – If the null hypothesis is not true (i.e. if there is a difference between the treatment and placebo), then the alternative hypothesis is true (Bland, 1996).
- **Visit effect**: Effect attributable to the different visits, or the passing of time (i.e. patients might be getting better because time passed without the treatment having had an effect (Grobler, 2006)
- **Treatment effect**: An effect attributable to the test treatment. Usually in a clinical trial inferred from a comparison of the test and control groups of the patients using observed results for a specified outcome measure (Grobler, 2006)
- **Visit by treatment interaction effect**: A situation in which the effect exerted by a treatment is influenced by the visit (e.g. one would say there was a visit by treatment interaction if the test-control treatment difference was in one direction for visit one and in the other direction for visit two (Grobler, 2006).

4.2) Baseline Analysis

This section shows a comparison of all baseline data for both groups (data collected prior to the first treatment) as displayed below.

Table 4.2.1 Disease severity

	Placebo	Treatment	Total
Mild	2 (25.0%)	6 (37.5%)	8
Moderate	4 (50.0%)	7 (43.8%)	11
Severe	2 (25.0%)	3 (18.8%)	5
	8	16	24

Fisher's exact test p-value = 1.000

Table 4.2.2 Drugs used

	Placebo	Treatment	Total
DMARD	2 (25.0%)	6 (37.5%)	8
None	3 (37.5%)	4 (25.0%)	7
NSAID	3 (37.5)	6 (37.5%)	9
	8	16	24

Fisher's exact test p-value = 0.8657

Table 4.2.3 Sex

	Placebo	Treatment
Female	5	13
Male	3	3
Total	8	16

Fischer's exact test p-value = 0.3618

Table 4.2.4 Age

	Mean	Std Dev	Minimum	Median	Maximum
Placebo	52.38	14.07	36.00	53.50	75.00

(N = 8)					
Treatment (N = 16)	55.56	9.66	40.00	54.00	72.00

Two sample t-test p- value = 0.5198

The baseline variables did not show a statistically significant difference between the treatment and placebo groups (p-value > 0.05). Therefore the two groups were comparable at baseline for disease severity, drug use, sex and age. These factors, therefore, should not be the cause of any major variations in the results of the two groups. Thus any changes in the treatment group relative to the placebo group that do occur would be attributable to the treatment. This fact allows the researcher to draw causal inferences with a higher degree of validity (Mouton, 2002).

4.3) Follow-up Over Time – Period Data:

This section shows a comparison of all the data collected prior to the first and seventh treatments and at the one-week (i.e. during the week after the nine treatments were completed) and one month follow-ups. The data have been tabulated, and then plotted in graph form, to show the progression of both groups over time. Results show the mean, median, standard deviation, minimum and maximum values.

4.3.1) Subjective Measures:

Table 4.3.1 Results of NRS 101

Placebo (N = 8)	Mean	Std Dev	Minimum	Median	Maximum
Baseline	35.94	21.71	2.50	40.00	65.00
After 6 treatments	29.69	20.33	7.50	25.00	60.00
After 9 treatments	24.06	17.78	2.50	22.50	55.00

Month later	30.31	18.87	0.00	31.25	55.00
Change from baseline to					
After 6 treatments	-6.25	22.36	-47.50	-6.25	30.00
After 9 treatments	-11.88	26.35	-57.50	-3.75	25.00
Month later	-5.63	28.31	-40.00	-5.00	32.50

Treatment (N = 16)

	Mean	Std Dev	Minimum	Median	Maximum
Baseline	40.16	24.26	2.50	36.25	80.00
After 6 treatments	27.91	20.87	0.00	32.50	70.00
After 9 treatments	23.28	17.12	0.00	25.00	60.00
Month later	16.94	13.79	0.00	16.25	40.00
Change from baseline					
After 6 treatments	-12.25	24.81	-50.00	-10.00	37.50
After 9 treatments	-16.88	18.94	-50.00	-10.00	7.50
Month later	-23.22	22.26	-67.50	-21.25	5.00

From table 4.3.1 it can be seen that the placebo group began the study with a mean NRS 101 value of 35.94, and the treatment group with a mean value of 40.16.

After the final treatment (i.e. after treatment nine) the mean NRS 101 value for the placebo group was 24.06 and for the treatment group it was 23.28. The improvement from before the initial treatment (baseline value) to after the final treatment for the placebo group was 11.88, and for the treatment group it was 16.88.

Therefore, it appears that both groups experienced a decrease in their pain (i.e. NRS 101 values decreased) during this period but that the improvement was slightly greater in the treatment group than in the placebo group.

At the one-month follow-up visit the mean NRS 101 value for the placebo group was 30.31 and for the treatment group it was 16.94. The improvement from before the initial treatment to the one-month follow-up for the placebo group was 5.63, whereas for the treatment group it was 23.22.

Therefore, it appears that the although the placebo groups' final mean NRS 101 value was less than their initial one, they had in fact worsened in the period between their one-week (i.e. after treatment nine) and one-month follow-ups. The treatment group, however, appears to have continued to improve over time.

The LLLT therefore appears to have produced a more lasting improvement in pain than the placebo treatment did.

Table 4.3.2 Results of DASH Questionnaire

Placebo (N = 8)	Mean	Std Dev	Minimum	Median	Maximum
Baseline	44.17	23.81	4.20	48.74	74.16
After 6 treatments	36.15	22.58	6.70	40.82	72.50
After 9 treatments	31.77	17.49	8.30	31.67	62.50
Month later	35.00	20.75	7.50	29.59	66.67
Change from baseline to					
After 6 treatments	-8.02	11.98	-31.70	-5.01	4.20
After 9 treatments	-12.40	18.69	-38.33	-8.75	14.20
Month later	-9.17	23.50	-53.33	-8.75	24.97
Treatment (N = 16)					
	Mean	Std Dev	Minimum	Median	Maximum

Baseline	43.58	24.67	5.80	36.67	89.17
After 6 treatments	34.63	19.77	6.60	34.59	60.83
After 9 treatments	27.23	18.95	5.00	25.42	65.83
Month later	25.57	20.72	7.50	20.00	75.00
Change from baseline to					
After 6 treatments	-8.95	13.62	-32.57	-7.95	24.93
After 9 treatments	-16.35	14.34	-57.97	-14.57	0.77
Month later	-18.01	19.00	-69.17	-12.50	5.03

Shown in table 4.3.2, the placebo group had an initial mean DASH value of 44.17 and the treatment group had a value of 43.48.

After their final treatment, the placebo group's mean DASH value was 31.77 and the treatment groups' was 27.23. The placebo group's improvement from their baseline reading (taken prior to the first treatment) to after their final treatment was 12.40 and the treatment group's was 16.35.

It therefore appears that both groups had an improvement in their daily functional ability (i.e. DASH values decreased), however the improvement was slightly greater in the treatment group than in the placebo group.

The placebo group's mean DASH value at their one-month follow-up was 35.00 and the treatment group's was 25.57. The placebo group's improvement from before their initial treatment to their one-month follow-up was 9.17 and the treatment groups' was 18.01.

There was some improvement the placebo group's mean DASH value between their baseline reading and the one taken at their one-month follow-up. Their mean DASH value, however, increased (worsened) between their one-week and one-month follow-ups.

In contrast the treatment group appears to continue to improve over time.

Therefore it appears that although there was an improvement in the daily functional ability of both groups, the LLLT received by the treatment group produced a more lasting effect than the placebo treatment did.

Table 4.3.3 Results of Morning Stiffness

Placebo (N = 8)

	Mean	Std Dev	Minimum	Median	Maximum
Baseline	51.43	68.17	0.00	18.93	174.00
After 6 treatments	47.07	76.86	0.00	15.67	228.60
After 9 treatments	48.94	80.47	0.00	16.72	240.00
Month later	37.25	43.80	0.00	22.50	120.00
Change from baseline to					
After 6 treatments	-4.36	50.82	-101.14	0.14	85.74
After 9 treatments	-2.49	54.10	-101.14	0.50	97.14
Month later	-14.18	31.61	-84.00	-0.65	19.00

Treatment (N = 16)

	Mean	Std Dev	Minimum	Median	Maximum
Baseline	59.46	74.12	0.00	28.57	242.80
After 6 treatments	31.77	41.01	0.00	12.72	120.00
After 9 treatments	13.14	18.29	0.00	4.50	60.00
Month later	9.41	22.41	0.00	0.79	90.00
Change from baseline to					
After 6 treatments	-27.70	59.16	-217.80	-12.28	47.14
After 9 treatments	-46.33	66.93	-215.70	-25.75	18.57
Month later	-50.06	65.90	-226.66	-26.17	0.00

Table 4.3.3 indicates that the placebo group began the study with a mean duration of morning stiffness of 51.43 minutes, and the treatment group with a mean value of 59.46 minutes.

After the final treatment the mean duration of morning stiffness for the placebo group was 48.94 minutes, and the treatment group's was 13.14 minutes. During the period between their first treatment and their one-week follow-up (after last treatment), the placebo group's morning stiffness decreased by 2.49 minutes and the treatment group's by 46.33 minutes.

Therefore, it appears that although both groups experienced a decrease in the duration of their morning stiffness during this period, the decrease was more marked in the treatment group than in the placebo group.

By the one-month follow-up when their final reading was taken, the placebo groups' morning stiffness had decreased by 14.18 minutes from the baseline reading taking it to a mean duration of 37.25 minutes. The treatment group's had decreased from their baseline reading by a 50.06 minutes to a mean duration of 9.41 minutes.

Therefore, it appears that the duration of both group's morning stiffness decreased during this period, the treatment group's improvement was, however, more pronounced. LLLT thus appears to have caused a more marked decrease in morning stiffness than the placebo did.

4.3.2) Objective Measure:

Table 4.3.4 Results of Algometer Readings

Placebo (N = 8)	Mean	Std Dev	Minimum	Median	Maximum
Baseline	6.42	2.54	3.60	5.50	10.65
After 6 treatments	5.19	2.27	2.50	5.05	8.60

After 9 treatments	5.31	2.56	1.90	4.80	10.80
Month later	5.86	1.86	2.20	6.35	8.20
Change from baseline to					
After 6 treatments	-1.23	1.67	-5.00	-0.65	0.10
After 9 treatments	-1.11	1.75	-4.20	-0.45	0.70
Month later	-0.56	1.67	-2.45	-0.98	2.30

Treatment (N = 8)

	Mean	Std Dev	Minimum	Median	Maximum
Baseline	4.76	2.00	2.30	4.23	8.90
After 6 treatments	6.01	2.42	3.10	5.90	13.00
After 9 treatments	6.63	3.07	2.50	6.73	14.00
Month later	6.82	2.85	3.15	6.70	12.50
Change from baseline to					
After 6 treatments	1.25	1.44	-0.25	0.80	4.80
After 9 treatments	1.87	1.89	-1.30	1.45	5.90
Month later	2.07	2.19	-0.85	1.80	6.25

From table 4.3.4 it can be seen that the placebo group's initial mean algometer reading was 6.42 lb/cm², and the treatment group's, was 4.76 lb/cm².

The placebo group's mean algometer reading after the final treatment was 5.31 lb/cm², having decreased by 1.11 lb/cm². The treatment group's was 6.63 lb/cm², having increased by 1.87 lb/cm². Therefore, it appears that during this period the amount of pressure that the placebo group's joints could be subjected to before pain was experienced decreased (i.e. the joints became more tender to pressure). The amount of pressure that the treatment group's joints could withstand increased (i.e. the joints became less tender to pressure).

By the one-month follow-up visit the amount of pressure that the placebo group's joints could withstand had decreased from their baseline reading by 0.56 lb/cm^2 to a pressure of 5.86 lb/cm^2. The treatment group's had increased from their baseline reading by 2.0 lb/cm^2 to a pressure of 6.82 lb/cm^2.

Therefore, it appears that the placebo group's joints could withstand slightly more pressure, before pain was experienced, than what they could at the one-week follow-up. However their joints could withstand less pressure at their one-month follow-up than what they could when their baseline reading was taken.

The treatment group's joints continued to be able to withstand progressively more pressure before pain was experienced. LLLT therefore appears to make the patients' joints less tender to pressure whilst the placebo did not appear to cause this improvement.

4.4) Analysis of Visit, Visit by Treatment Interaction and Treatment Effects:

From the analysis of the visit, visit by treatment and treatment effects, it was determined whether the Null Hypothesis (Ho) or the Alternative Hypothesis (HA) had to be applied.

a) The Subjective clinical findings,
Ho: There is no difference between the two groups in terms of the subjective clinical findings on analysis of the data.
Ha: There is a difference between the two groups in terms of the subjective clinical findings on analysis of the data.

b) Objective clinical findings,

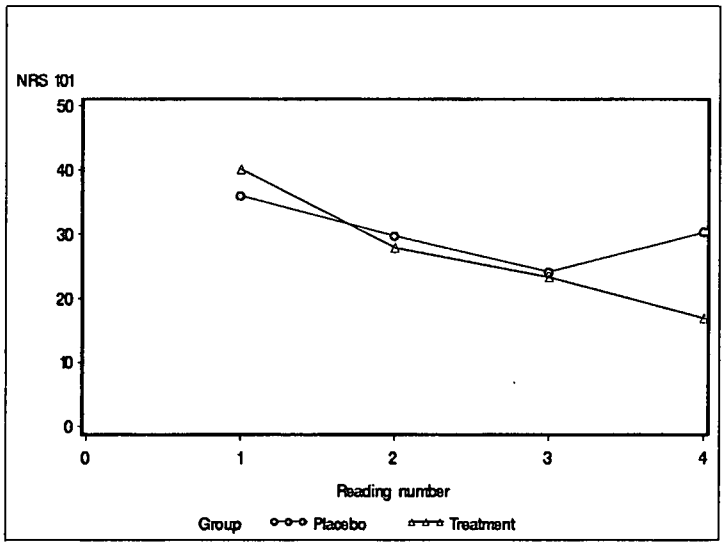
HO: There is no difference between the two groups in terms of the objective clinical findings on analysis of the data.
Ha: There is a difference between the two groups in terms of the subjective clinical findings on analysis of the data.

The null hypothesis shall be rejected at the α level of significance (α = 0.05) if $p \leq \alpha$. Therefore, if the p-value for an outcome is found to be less than or equal to 0.05, it is concluded that there is a statistically significant difference between the two groups for the outcome tested. Conversely, if the p-value for an outcome is found to be greater than 0.05, it is concluded that there is no statistically significant difference between the two groups for the outcome tested.

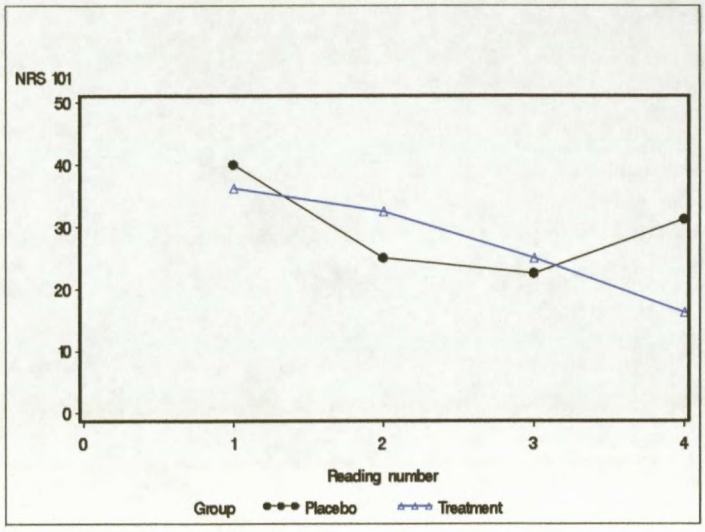
4.4.1) Subjective Measures:

Table 4.4.1 p-values for NRS 101

Outcome	Effect	p-value
NRS 101	Visit	0.0034
	Visit by Treatment Interaction	0.2210
	Treatment	0.6624



Graph 4.4.1 Mean NRS score over time



Graph 4.4.2 Median NRS score over time

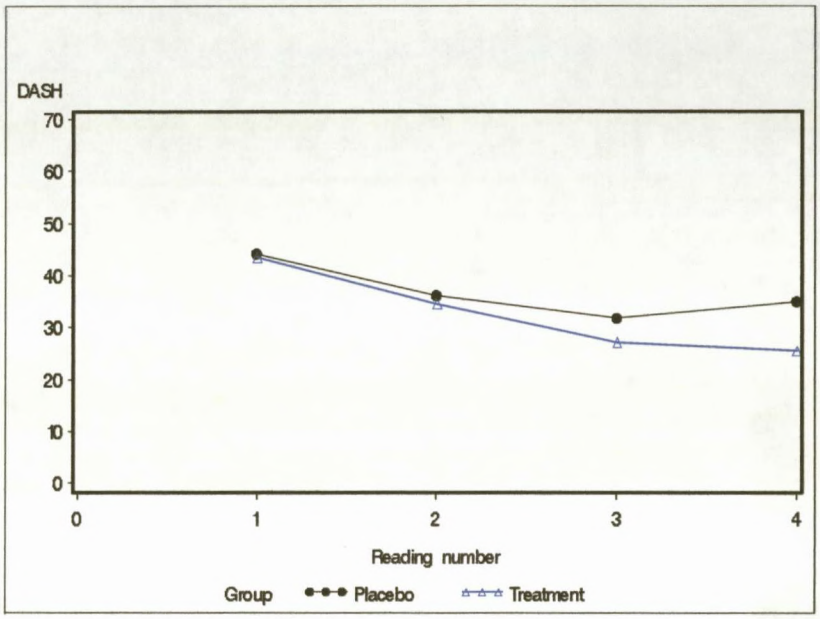
As evidenced by the above table and graphs, the NRS 101 values have shown a statistically significant visit effect (p = 0.0034), but no statistically significant visit by treatment interaction effect (p = 0.2210) or treatment effect (p = 0.6624). Both groups thus improved over time (shown by the statistically significant visit effect, p = 0.0034). This improvement did not, however, differ between the treatment and placebo groups (i.e. the placebo group improved as much as the treatment group).

The NRS 101 values improved in both groups for the first three readings, however the placebo group's values then deteriorated again by the final reading whilst the treatment group values continued to improve over time.

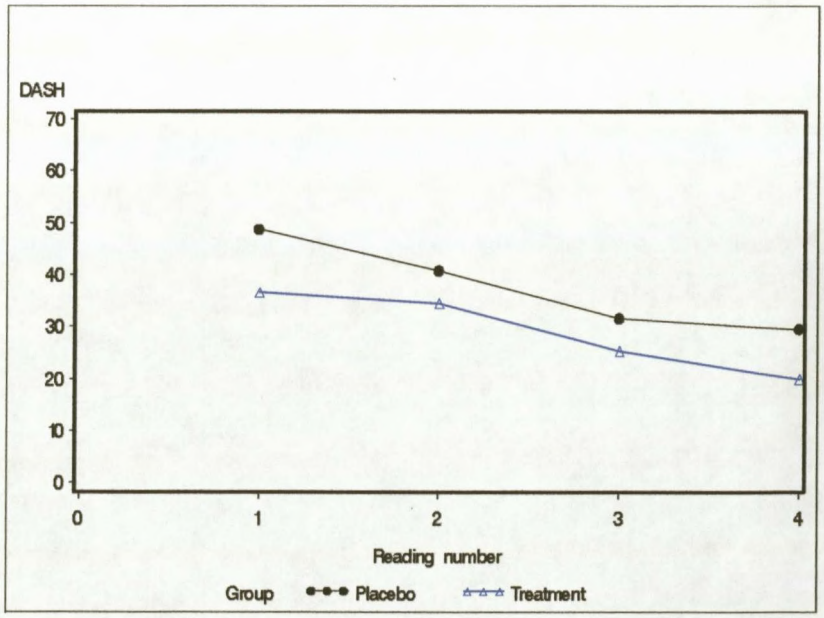
The p-value for the difference between the baseline and final reading is 0.1093. This is not statistically significant, thus showing that by the end of the research protocol the patients had not achieved a statistically significant improvement in their pain. The Null Hypothesis is thus accepted for NRS 101.

Table 4.4.2 p-values for DASH questionnaire

Outcome	Effect	p-value
DASH	Visit	0.0053
	Visit by Treatment Interaction	0.7440
	Treatment	0.6288



Graph 4.4.3 Mean DASH score over time



Graph 4.4.4 Median DASH score over time

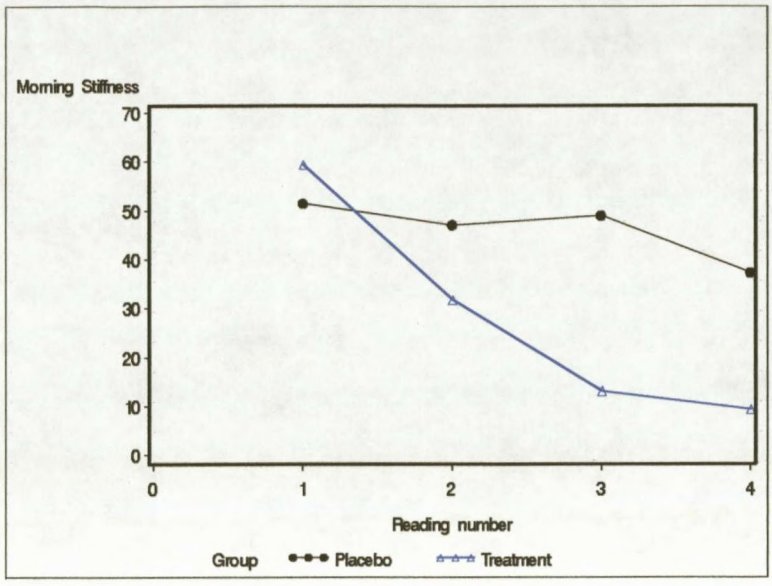
The above table and graphs indicate that the DASH questionnaire showed only a statistically significant visit effect (p = 0.0053). There was no statistically significant visit by treatment interaction effect (p = 0.7440) or treatment effect (p = 0.6288).

If the difference between baseline and the last value are analysed, the p-value for a difference between treatments is 0.3310, which is not considered to be significant.

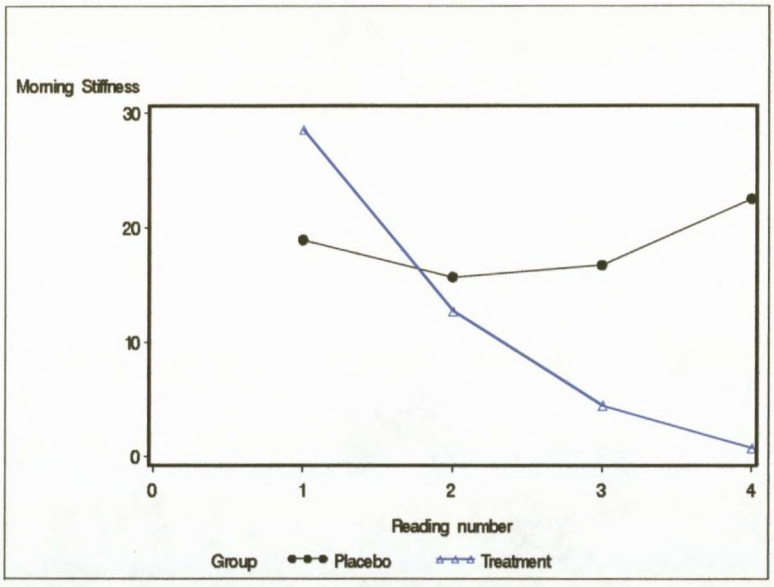
Both groups improved over time (shown by the statistically significant visit effect). But since this improvement occurred in both the treatment and the placebo group, the improvement in the patient's daily functional ability caused by the LLLT was not found to be statistically significantly better than that caused by the placebo.
The Null Hypothesis is thus accepted for the DASH questionnaire.

Table 4.4.3 p-values for Duration of morning stiffness

Outcome	**Effect**	**p-value**
Morning stiffness	Visit	0.00183
	Visit by Treatment Interaction	0.1691
	Treatment	0.3730



Graph 4.4.5 Mean morning stiffness over time



Graph 4.4.6 Median morning stiffness over time

The above table and graphs indicate that the duration of morning stiffness experienced by the patients showed a statistically significant visit effect (p = 0.0183). There was no statistically significant visit by treatment interaction effect (p = 0.1691) or treatment effect (p = 0.3730). This means, that although there was a change over time for both groups (which was more marked for the treatment group), it did not reach a level of statistical significance.

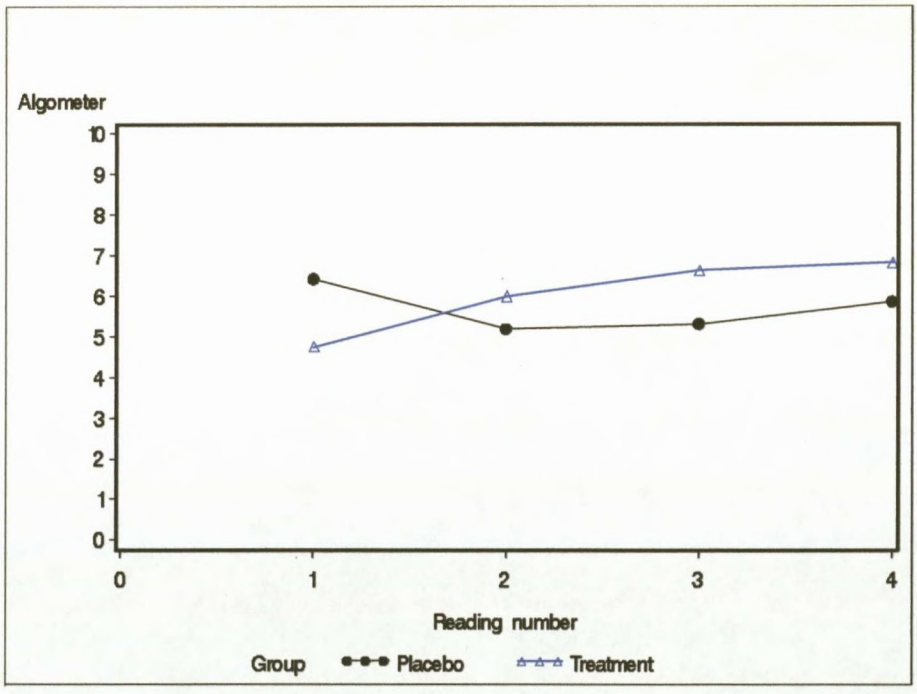
If only the difference between the baseline and the last value is analysed, the p-value for a difference between treatments is 0.1621, which is not statistically significant.

The Null Hypothesis is thus accepted for the duration of morning stiffness.

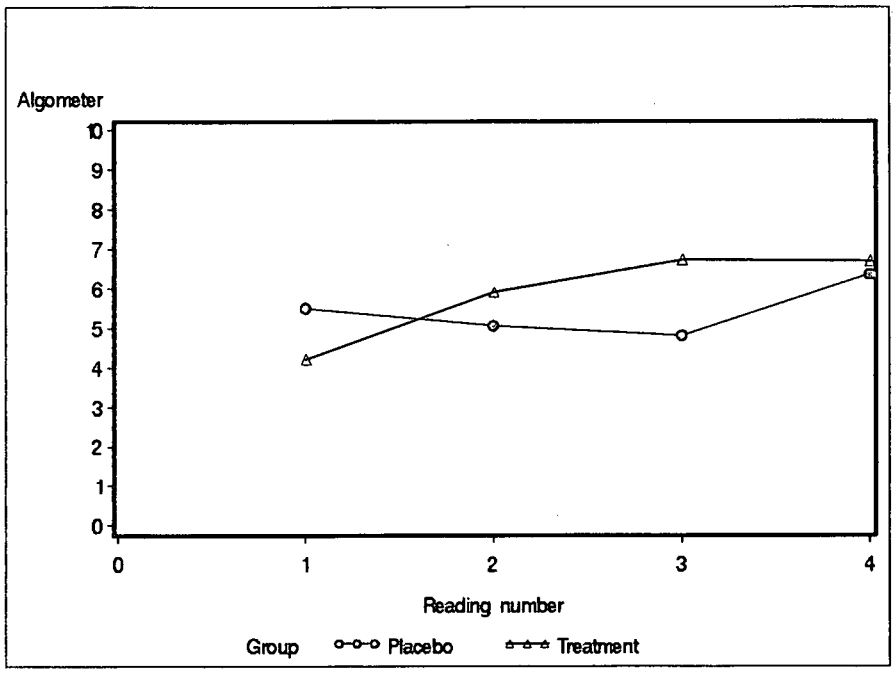
4.4.2) Objective Measure:

Table 4.4.4 p-value for algometer readings

Outcome	Effect	p-value
Algometer	Visit	0.1779
	Visit by Treatment Interaction	0.0010
	Treatment	0.7189



Graph 4.4.7 Mean algometer reading over time



Graph 4.4.8 Median algometer reading over time

As indicated by the above table and graphs, the algometer readings did not show a statistically significant difference in the visit effect (p = 0.1779) or treatment effect (p = 0.7189). There was however a statistically significant visit by treatment interaction effect (p = 0.0010), meaning that at some visits the treatment effect was different than at some other visits.

If we only take the difference between baseline and the last value, the p-value for a difference between treatments is 0.0069, which is statistically significant. The Null Hypothesis is thus accepted for the algometer readings.

4.5) Summary:

The treatment and placebo groups were found to be comparable at baseline for disease severity, drug use, sex and age.

The results of the study were found to suggest that there was no statistically significant difference in the treatment effect between the treatment and placebo groups The visit effect was statistically significant for most outcomes, meaning that there was a significant improvement from one visit to the next

but that neither the placebo nor the laser treatment was significantly more effective than the other.

The treatment group showed better improvement, but not statistically significant, for all the outcomes than the placebo did.

CHAPTER FIVE

Discussion of Results

5.1) Introduction:

In this chapter, the results of the subjective and objective findings are discussed, and comparisons are made between this study and other related studies.

5.2) Discussion of Results:

The treatment group had a mean age of 55.56 years and the placebo group had a mean age of 52.38 years. The onset of RA typically starts between the ages of 20 and 60 with a peak occurrence between 40 and 50 years of age (Haslett et al., 2001). The mean age group of both groups therefore lies within the normal range but is a bit higher than the internationally set peak age group.

The treatment group was made up of 16 patients in total, 13 of which were female and 3 were male (female:male ratio is 4.3:1). The placebo group had 8 patients, with 5 of these being female and 3 being male (female:male ratio is 1.67:1). Internationally the female to male ratio in the 20 to 40 year age group is 3:1 whereas after 40 years of age the ratio is approximately 1:1 (Yochum et al., 1996).

The mean age group for the treatment group was 55.56 years and for the placebo group it was 52.38 years (See table 4.2.4). As means for both groups were greater than 40 years of age, we would have expected the male to

female ratio to have been 1:1 for both groups (based on international trends) (Yochum et al., 1996). We can, however, see that the male to female ratio in this study differed slightly from the internationally set gender ratio.

This is also in contrast to the female to male ratio in South Africa that has been estimated at approximately 3.7:1(Mody et al., 1989). This should not, however, have had a large impact on the results, as there are no differences in terms of clinical signs, severity or radiographic changes between the sexes (Yochum et al., 1996).

Of the patients in the treatment group 37.5% were taking a DMARD, 37.5% were taking an NSAID and 25.0% were taking no medication. In the placebo group 25.0% of the patients were taking a DMARD, 37.5% were taking an NSAID and 37.5% were taking no medication. The selection of medication is patient dependent and would therefore vary accordingly between studies.

5.2.1) The Subjective Clinical Findings:

5.2.1.1) NRS 101

The NRS 101 values have shown a statistically significant visit effect ($p = 0.0034$), but no statistically significant visit by treatment interaction effect ($p = 0.2210$) or treatment effect ($p = 0.6624$) (see table 4.4.1). Both groups thus improved over time (shown by the significant visit effect, $p = 0.0034$). This improvement did not, however, differ significantly between the treatment and placebo groups.

The NRS 101 values improved in both groups for the first 3 readings, however the placebo groups' values then deteriorated again by the final reading whilst the treatment group values continued to improve over time.

The p-value for the difference between the baseline and final reading is 0.1093, which is not statistically significant showing that by the end of the research protocol the patients had not achieved a significant improvement in

their pain. Perhaps a larger sample size may have produced a statistically significant difference.

The Null Hypothesis is thus accepted for NRS 101, i.e. there is no difference between the two groups for the outcome of the NRS 101.

The pain in the MCP and PIP joints of the patients who received LLLT decreased. The basis for this effect is based on the fact that diseased or damaged tissues releases superoxide radicals, an inflammatory mediator, which combines with arachidonic acid to form prostaglandin E2 (PgE2). This converts adenotriphosphate (ATP) into cyclic adenomonophosphate (cyclic AMP) that in turn results in an increased sensitivity of the nociceptors resulting in increased levels of pain. Irradiation with low level laser results in the release of superoxide dismutase (SOD) that scavenges the superoxide radicals which decreases the amount of PgE2 produced. Low-level laser also causes a photochemical reaction, which converts prostaglandins to prostacyclin endoperoxide with a resultant decrease in the sensitivity of the nociceptors and thus further reducing pain (Liggins, 2002).

The lack of a significant decrease in the NRS 101 values for the treatment group relative to the placebo group may have been due to the fact that both groups were interacting with the researcher frequently over a short period of time while the treatments were taking place. As a result of this the patients may have been exhibiting the Hawthorne effect, whereby they showed improvement simply because they were getting special attention, and not necessarily because of the treatment they were receiving (Bailey, 1997). Also because they perceived that they were receiving treatment, they may have convinced themselves that they were improving.

However during the month after the 9 treatments, the placebo group may have found that they had not improved as much as they had first perceived and so during this period when they were not exposed to the researcher, their "improvement" regressed. In contrast the treatment group may have found

that they had in fact improved, and thus during this 1 month period they may have continued to improve as a result of the treatment.

As stated above, both groups experienced a decrease in the intensity of their perceived pain. This correlates with the findings of studies done by Bliddal et al., (1987), Heussler et al., (1993) and Johannsen et al., (1994). It should however be noted that in the studies done by Heussler et al., (1993) and Johannsen et al., (1994) the patients contralateral hand was used as the placebo and this disregarded the possible systemic effects of laser that could have had an analgesic effect on the contralateral hand (Baxter, 1994).

It should however be noted that although both groups experienced pain relief, the decrease in pain was more marked (though not significantly so) in the treatment group. A study done by Walker et al., (1987) noted a significant decrease in pain in the treatment group as compared with the placebo group. The study had a sample size of 72 patients and it may be that the larger sample size used in this study led to a statistically significant difference.

Brosseau et al., (2002) found in their Cochrane review of similar studies that LLLT caused a reduction in pain by 70% in the treatment group relative to the placebo group. Whilst Hall et al., (1994) stated that the patients in their study did not feel that the LLLT had decreased their pain.

5.2.1.2) DASH Questionnaire

The DASH questionnaire showed only a statistically significant visit effect ($p = 0.0053$). There was no statistically significant visit by treatment interaction effect ($p = 0.7440$) or treatment effect ($p = 0.6288$) (see table 4.4.2).

If the difference between baseline and the last value are analysed, the p-value for a difference between treatments is 0.3310, which is not considered to be significant.

Both groups improved over time (shown by the significant visit effect). But since this improvement occurred in both the treatment and the placebo group, the improvement in the patient's daily functional ability caused by the LLLT was not found to be significantly better than that caused by the placebo. The Null Hypothesis is thus accepted for the DASH questionnaire.

Studies done by Heussler et al., (1993) and Hall et al., (1994) also found that there was no statistically significant improvement in the patients' functional daily ability. The Cochrane review conducted by Brosseau et al., (2002), also concurred with these findings.

In addition to the decreased pain in the treated joint (as discussed in 5.2.1.1), the reduction in PG-E2 (which promotes inflammation by potentiating the effects of other inflammatory mediators) also results in a decrease in inflammation in the joint. As a result of the decreased pain and inflammation the patient may be able to perform activities of daily living with greater ease, thus resulting in a decrease in their DASH score.

The perceived improvement in the functional daily ability of the two groups may have been due to a similar reason as outlined in 5.2.1.1. However in this case the difference in the improvement between the two groups was not as great and the placebo groups' improvement did not regress during the month after their final treatment. The less marked improvement in this outcome seen in both groups may be due to the fact that the irreversible joint changes (e.g. joint erosion and pannus formation) (Kelly et al., 1993; Hart et al., 1987;Haslett et al., 2001) associated with RA may have acted as a limiting factor to the amount of functional improvement that was possible.

5.2.1.3) Duration of Morning Stiffness

The duration of morning stiffness experienced by the patients showed a statistically significant visit effect (p = 0.0183). There was no statistically significant visit by treatment interaction effect (p = 0.1691) or treatment effect (p = 0.3730) (see table 4.4.3). This means, that although there was a change over time for both groups (which was more marked for the treatment group), it did not reach a level of statistical significance.

If only the difference between baseline and the last value are analysed, the p-value for a difference between treatments is 0.1621, which is not significant. The Null Hypothesis is thus accepted for the duration of morning stiffness.

The decrease in the duration of morning stiffness was, however, more marked (though not enough to be statistically significant) in the treatment group
In the Cochrane review done by Brosseau et al., (2002), they also noted a greater decrease (of 27,5 minutes) in the duration of morning stiffness for the treatment group relative to the placebo group.

Morning stiffness occurs as a result of the accumulation of the inflammatory substances in the joint (Kelly et al., 1999). Therefore LLLT may decrease morning stiffness by decreasing the inflammation in the joint (by the mechanism discussed in 5.2.1.2).

The perceived improvement in the duration of morning stiffness of the two groups may attributable to a similar reason as outlined in 5.2.1.1.
It should, however be taken into account that during the treatments the researcher was moving the patients' fingers and hand in the process of applying the laser to each aspect of the MCP and PIP joints, and this may have acted as a very basic mobilisation of the joints. Movement of the joints may have helped dissipate the inflammation and thus helped to decrease the duration of morning stiffness Kelly et al., (1993).

5.2.2) The Objective Clinical Finding:

5.2.2.1) Algometer

The algometer readings did not show a statistically significant difference in the visit effect (p = 0.1779) or treatment effect (p = 0.7189) (see table 4.4.4). There was however a statistically significant visit by treatment interaction effect (p = 0.0010), meaning that at some visits the treatment effect was different than at some other visits.

If we only take the difference between baseline and the last value, the p-value for a difference between treatments is 0.0069, which is statistically significant. The Null Hypothesis is thus accepted for the algometer readings.

Previous studies have not discussed the effects of LLLT on algometer readings. The patients perceived pain is measured by the NRS 101 and inflammation is reflected by the duration in morning stiffness. It would be expected that as the patients pain and inflammation decreased, the amount of pressure that could be applied to the joint before they felt pain (indicated by their algometer readings) should increase.

5.3) Summary:

The lack of a significant improvement in the readings for the treatment group relative to the placebo group may have been due to the fact that both groups were interacting with the researcher frequently over a short period of time while the treatments were taking place. As a result of this the patients may have been exhibiting the Hawthorne effect, whereby they showed improvement simply because they were getting special attention, and not necessarily because of the treatment they were receiving (Bailey, 1997). They would also have perceived that they were receiving treatment, they may have convinced themselves that they were improving.

However during the month after the 9 treatments, the placebo group may have found that they had not improved as much as they had first perceived and so during this period when they were not exposed to the researcher, their "improvement" regressed. In contrast the treatment group may have found that they had in fact improved, and thus during this 1 month period they may have continued to improve as a result of the treatment.

CHAPTER SIX

Conclusions and Recommendations

6.1) Conclusions:

The study consisted of 24 patients divided into two groups (16 patients in the treatment group and eight patients in the placebo group). The patients were assigned to the different groups based on the outcome of their DASH Questionnaire and their primary medication. Group A consisted of those who received LLLT (i.e. the treatment group) while group B consisted of those who were treated with a laser that was not turned on (i.e. the placebo group). All patients underwent an extensive medical history, physical and orthopedic examinations, from which their diagnosis of RA affecting the hands was confirmed.

All patients received three treatments a week for three consecutive weeks and had a one week and one month follow-up visit.

The results of the study suggest that there was no statistically significant difference in the treatment effect between the treatment and placebo groups The visit effect was statistically significant for most outcomes, meaning that there was a significant improvement from one visit to the next but that neither the placebo nor the laser treatment was significantly more effective than the other.

The treatment group showed better improvement (but not significantly so) for all the outcomes than the placebo did. Therefore, laser therapy may be more effective than the placebo in the management of the hand symptoms of rheumatoid arthritis. Further investigations involving a larger sample size, a

longer treatment period and different laser parameters may produce statistically significant results.

6.2) Recommendations:

For further studies, the following recommendations may be made:

1. A larger sample size may improve the statistical significance of some of the results. This is due to the fact that larger sample groups result in more accurately reflective statistics (Grobler, 2006).
2. A longer treatment period (three treatments a week for at least four consecutive weeks) may result in better results as the effects seem to improve over time.
3. A two-month follow-up visit may also reveal a greater difference between the two groups. As even by the one-month follow-up a divergence of the two groups results as generally seen, with the treatment group continuing to improve whilst the placebo group started to regress.
4. A hand –specific (i.e. not a general upper limb) assessment of the patient's daily functional ability may highlight a more marked difference between the two groups. Even though the DASH questionnaire looks closely at activities of daily living that involve hand function, there are also questions that look at elbow and shoulder function. Therefore a questionnaire that focuses soley on hand function would be more advisable.
5. The use of different laser settings (e.g. wavelength, etc) may also impact the effectiveness of the laser treatment as the most effective laser values have yet to be established. Thus even by simply altering one laser parameter, one may get better results as it may cause a greater decrease in pain and / or inflammation.
6. Treatment and placebo groups of an equal size containing equal proportions of mild, moderate and severely affected patients may aid in

making the two groups even more comparable at baseline (Mouton, 2002).

Appendix A

Dear Participant

Welcome to my research project

TITLE OF RESEARCH:

A pragmatic controlled clinical trial investigating the efficacy of low-level laser therapy as a part of the palliative management of the hand symptoms of rheumatoid arthritis.

NAME OF RESEARCH STUDENT:

Keriann Stagg Contact number⊗031) 2042 2205

NAME OF RESEARCH SUPERVISOR:

Dr. Heidi Kretzmann Contact number: (031) 204 2244

You have been selected to take part in a study regarding the effectiveness of laser therapy as treatment for rheumatoid arthritis. 24 patients will be required to take part in this study. There will be two groups, one will receive laser treatment of the hands and the second group will receive a placebo treatment. Each patient will have an equal chance of being in either group.

INCLUSION CRITERIA:

In order to take part in this study you must be between the ages of 20 and 75 and must meet certain diagnostic criteria that are laid down by the American Rheumatism Association.

EXCLUSION CRITERIA:

You will be excluded from the study if you have any other inflammatory arthritic diseases, are pregnant or if you have infection, hemorrhage or cancer of the hand.

PROCEDUES:

At the first consult, which will be at the Durban Institute of Technology Chiropractic Day Clinic, you will be scanned for suitability as a participant based on a case history, physical examination and a hand and wrist regional examination. You will be asked to complete a questionnaire and certain simple tests will be performed on your hand at the first visit, seventh visit, and at the one week and one month follow-ups.

TREATMENTS:

Week 1: 3 treatments

Week 2: 3 treatments

Week 3: 3 treatments

Week 4: follow-up (no treatment)

Week 7: follow-up (no treatment)

RISKS/DISCOMFORTS:

Studies investigating the effects of laser in the treatment of rheumatoid arthritis have reported either no side effects or at worst a mild burning sensation at the site being treated. However in this study a low-level cold laser will be used and as a result this should prevent the burning sensation from occurring.

BENEFITS:

It is hypothesized in the literature that the laser is responsible for positive clinical effects in inflammatory processes; therefore it may provide some relief of your symptoms.

NEW FINDINGS:

The results of this study will be used to help develop a more effective approach to the treatment of rheumatoid arthritis.

REASONS WHY YOU MAY BE WITHDRAWN FROM THIS STUDY WITHOUT YOUR CONSENT:

You may be removed from this study without your consent if any of the following occur during the treatment or follow-up period.

1) Acute flare up of your arthritis.
2) Any change in the drugs or treatment that you are receiving for your arthritis.
3) Significant trauma to your hand.
4) You miss your appointments.

REMUNERATION AND COSTS OF THE STUDY:

You will not be paid for participating in the research, however the treatment will be performed free of charge. Those falling into the placebo group will receive at least two free treatments should they wish.

CONFIDENTIALITY:

All information will be coded so that only the research student and supervisor will know from whom the information was obtained. Your identity will not be disclosed in any publication.

PERSONS TO CONTACT WITH PROBLEMS OR QUESTIONS:

If you have any questions on any aspect of this study please feel free to contact my research supervisor or myself at the above mentioned details. Alternatively should you wish you cam contact the Faculty of Research and Ethics Committee as per Mr. Vikesh Singh (031) 204 2701.

Thank You.

Yours sincerely,

Keriann Stagg	Dr. Heidi Kretzmann
(Research student)	(Supervisor)

DURBAN INSTITUTE of TECHNOLOGY

INFORMED CONSENT FORM

(To be completed by patient / subject)

Date :

Title of research project :

A Pragmatic Controlled Clinical Trial Investigating the Efficacy of Low-Level Laser Therapy as a Part of the Palliative Management of the Hand Symptoms of Rheumatoid Arthritis.

Name of supervisor : Dr. Heidi Kretzmann
Tel : (031) 204 2244
Name of research student : Keriann Stagg
Tel : (031) 204 2205

Please circle 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 informatio before signing

Please Print in block letters:

Patient /Subject Name:_____ Signature: _____

Parent/ Guardian:_____ Signature:_____

Witness Name:_____ Signature:_____

Research Student Name:_____ Signature:_____

Appendix C: 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

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 D: 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

DURBAN INSTITUTE of TECHNOLOGY

Appendix E

Hand and wrist regional examination

Patient:_____ File no:_____ Date:_____
Intern:_____ Signature:_____
Clinician:_____ Signature:_____

Observation:

		Right	Left
1.	bony and soft tissue contours		
2.	hand posture		
3.	vasomotor changes		
4.	scars, skin creases, and muscle wasting		
5.	fingernails		
6.	dominant hand		

Palpation:

Posterior surface			Right	Left
1.	Anatomical snuff box			
2.	Carpal bones			
3.	Metacarpal bones			
4.	Phalanges			
5.	Pulses and capillary refill			
6.	Radial styloid			
7.	Radial (Lister's) tubercle			
8.	Ulnar styloid			
9.	6 extensor tendon tunnels		Right	Left
	i.	Abd poll long		
		Ext poll brev		
	ii.	ECRB		
		ECRL		
	iii.	Ext poll long		
	iv.	Ext digit		
		Ext index		
	v.	Ext digiti mini		
	vi.	ECU		

Anterior surface		Right	Left
1.	Tendons (Lat to med)		
	a. Flexor carpi radialis		
	b. Flexor poll longus		
	c. Flexor digit super		
	d. Flexor digit profund		
	e. Palmaris long		
	f. Flexor carpi ulnaris		
2.	Palmar fascia and intrinsic muscles		

Active movements

		Right	Left
1.	Pronation (85-90°)		
2.	Supination (85-90°)		
3.	Ulnar deviation (15°)		
4.	Radial deviation (30-45°)		
5.	Wrist flexion (80-90°)		
6.	Wrist extension (70-90°)		
7.	Finger movements		

Passive movements

	Right	Left
Tissue stretch		
Tissue stretch		
Bone		
Bone		
Tissue stretch		
Tissue stretch		

Resisted isometric movements

			Right	Left
1.	Flexion			
2.	Extension			
3.	Radial dev			
4.	Ulnar dev			
5.	Finger	Opposition		
		Adduction		
		Abduction		

Functional movements

Gross Grip Strength

		Right	Left
1.	fist grip		
2.	cylinder grip		
3.	hook grip		
4.	sphere grip		

Precision Grip Strength

	Right	Left
pinch		
chuck		
key		

Special tests

		Right	Left
1.	Finkelstein's test		
2.	Tinel's		
3.	Phalan's test		
4.	Reverse phalan's test		
5.	Allen's test		
6.	Froment's sign		
7.	Watson's test		
8.	Scaphoid compression test		
9.	Lunatotriquetral ballottment test		
10.	Bunnel littler test		
11.	Tight retinacular test		
12.	Ligament stability		

Joint play movements

Hand and fingers

			Right	Left
1.	MCP and PIP + DIP	Long axis extension		
		AP, PA glide		
		Rotation		
		Side glide		
2.	Distal inter-metacarpals	AP, PA glide		
		Rotation		

Wrist

			Right	Left
1.	Long axis extension			
2.	AP glide			
3.	Carpal extension			
4.	Carpal flexion			
5.	Ulnar deviation			
6.	Radial deviation			
7.	Ul-men-triq AP+ PA glide			
8.	Inf rad-ulnar rotation	AP, PA glide		
		Rotation		

Appendix F

CRITERIA FOR THE DIAGNOSIS OF RHEUMATOID ARTHRITIS (American Rheumatism Association 1988 revision). (Boers et al., 1999)

Any four of the following must be present to classify patients as having rheumatoid arthritis.

- Morning stiffness for > one hour *
- Arthritis of three or more joint areas *
- Arthritis of hand joints (wrists, metacarpophalangeal or proximal interphalangeal joints) *
- Symmetric arthritis *
- Rheumatoid nodules
- Serum rheumatoid factor
- Radiographic changes (hand x-ray changes typical of rheumatoid arthritis must include erosions or unequivocal bony decalcification).

* Must be present for six weeks or longer

Appendix G

Criteria for Classification of Functional status in Rheumatoid Arthritis

The patient had to have a functional capacity of II or III according to the Classification of Functional Status in Rheumatoid Arthritis. (Appendix M).

- Class I: Completely able to perform usual activities of daily living (self-care, vocational and avocational[1]).
- Class II: Able to perform usual self-care[2] and vocational activities, but limited in avocational activities.
- Class III: Able to perform usual self-care activities, but limited in vocational and avocational activities.
- Class IV: Limited in ability to perform usual self-care, vocational, and avocational activities.

---

[1] Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex – specific.

[2] Usual self-care activities include dressing, feeding, bathing, grooming, and toileting.

Appendix H
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 I

THE DASH QUESTIONNAIRE

INSTRUCTIONS:
This Questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer every question, based on your condition in the past week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please estimate on which response would be the most accurate.

DISABILITIES OF THE ARM, SHOULDER AND HAND

ase rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
Open a tight or new jar.	1	2	3	4	5
Write	1	2	3	4	5
Turn a key.	1	2	3	4	5
Prepare a meal	1	2	3	4	5
Push open a heavy door.	1	2	3	4	5
Place an object on a shelf above your head.	1	2	3	4	5
Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
Garden or do yard work.	1	2	3	4	5
Make a bed	1	2	3	4	5
Carry a shopping bag or briefcase.	1	2	3	4	5
Carry a heavy object (over 10 lbs).	1	2	3	4	5
Change a lightbulb overhead.	1	2	3	4	5
Wash or blow dry your hair.	1	2	3	4	5
Wash your back.	1	2	3	4	5
Put on a pullover sweater.	1	2	3	4	5
Use a knife to cut food.	1	2	3	4	5
Recreational activities which require little effort (e.g., cardplaying, knitting, etc.)	1	2	3	4	5
Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.)	1	2	3	4	5
Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
Manage transportation needs (getting from one place to another).	1	2	3	4	5
Sexual activities.	1	2	3	4	5

Disabilities of the Arm, Shoulder and Hand

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
2 During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

ase rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
Arm, shoulder or hand pain	1	2	3	4	5
Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
Weakness in your arm, shoulder or hand.	1	2	3	4	5
Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

ring DASH function/symptoms: Add up circled responses (items 1-30); subtract 30; divide by 1.20 = DASH score. If there are onses missing, see detailed instructions.

Appendix J

DURATION OF MORNING STIFFNESS

DAY OF THE WEEK	NUMBER OF MINUTES
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
average	

DAY OF THE WEEK	NUMBER OF MINUTES
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
average	

DAY OF THE WEEK	NUMBER OF MINUTES
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
average	

DAY OF THE WEEK	NUMBER OF MINUTES
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
average	

DAY OF THE WEEK	NUMBER OF MINUTES
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	
average	

Appendix K

ALGOMETER READINGS

Reading from the most painful joint	
Reading from the least painful joint	
Average	

Reading from the most painful joint	
Reading from the least painful joint	
Average	

Reading from the most painful joint	
Reading from the least painful joint	
Average	

Reading from the most painful joint	
Reading from the least painful joint	
Average	

Journal Article

Abstract:

Aim: This research was aimed at determining the efficacy of low-level laser therapy as a part of the palliative management of the hand symptoms of rheumatoid arthritis.

Methods: Twenty-four patients suffering with rheumatoid arthritis were assigned to one of two groups based on the outcome of the DASH questionnaire and their primary medication. Group A received low-level laser therapy (LLLT) (20mW, 675 nm, 5000HZ) whilst group B was treated with a laser that was not turned on. The proximal interphalangeal (PIP) joints and metacarpophalangeal (MCP) joints of all 5 digits of the most severely affected hand were treated three times a week for three weeks. Subjective measures consisted of the Numerical Rating Scale-101 (NRS-101), Disability of the Arm, Shoulder and Hand (DASH) Questionnaire and the duration of morning stiffness. Objective measures consisted of algometer readings

Results: The treatment and placebo groups were found to be comparable at baseline for disease severity, drug use, sex and age. The results of the study were found to suggest that there was no statistically significant difference in the treatment effect between the treatment and placebo groups The treatment group, however, showed better improvement (but not statistically significant) for all the outcomes than the placebo did.

Conclusions: Therefore, laser therapy may be more effective than the placebo in the management of the hand symptoms of rheumatoid arthritis.

Introduction:

Rheumatoid arthritis (RA) is a chronic syndrome characterised by non-specific, usually symmetric inflammation involving the peripheral joints, which may result in progressive destruction of articular and periarticular structures, with or without generalised manifestations (Boers et al., 1999; Haslett et al. 2001; Yochum et al., 1996).

LLLT may offer a viable treatment option as its application theoretically supports and suggests that the physiological effects of LLLT are biostimulation, improved metabolism, increased cell metabolism, improved blood circulation, vasodilatation, analgesic effects, anti-inflammatory and anti-edematous effects; all of which are desired in the treatment of RA (Baxter, 1994; Kahn, 1994, Liggins, 2002).

These clinical effects are based on the fact that diseased or damaged tissues release superoxide radicals, an inflammatory mediator, which combines with arachidonic acid to form prostaglandin E2 (PgE2). This converts adenotriphosphate (ATP) into cyclic adenomonophosphate (cyclic AMP) that in turn results in an increased sensitivity of the nociceptors resulting in increased levels of pain. Irradiation with LLLT results in the release of superoxide dismutase (SOD) that scavenges the superoxide radicals, which decreases the amount of PgE2 produced from the arachidonic acid and ultimately reduces pain (Liggins, 2002). This effect of LLLT is further enhanced by a photochemical reaction, which converts prostaglandins to

prostacyclin endoperoxide with a resultant decrease in the sensitivity of the nociceptors and thus further reducing pain (Liggins, 2002).

The reduction in PG-E2 (which promotes inflammation by potentiating the effects of other inflammatory mediators) also results in a decrease in inflammation in the joint. Thus there should also be a decrease in the duration of morning stiffness, which occurs as a result of the accumulation of the inflammatory substances in the joint) (Kelly et al., 1993).

There is however controversy within in the literature as to the efficacy of LLLT (Asada et al., 1991; Bliddal et al., 1987; Goats. et al., 1996; Hal et al., 1994; Heussler et al., 1993; Johannsen et al., 1994; Palmagren et al., 1989; Walker et al., 1987). This is partially attributable to the lack of consensus regarding the methodology applied in these studies.

This research was therefore aimed at determining the efficacy of low-level laser therapy as a part of the palliative management of the hand symptoms of rheumatoid arthritis.

Patients and Methods:

Twenty-four patients with rheumatoid arthritis (RA) (diagnosis made according to the criteria of the American Rheumatism association) were included in the study.

The patients underwent a case history, physical examination and a hand and wrist regional examination. They were subsequently required to sign an informed consent form if they were deemed to fit the criteria of the study and included.

Patients were allocated to different categories (groups) based on the outcome of the DASH (Disabilities of the arm, shoulder and hand) questionnaire and their primary medication. For the purpose of this study a score on the DASH questionnaire of 0-33 constituted a mild disability, 34-66 a moderate disability and 67-100 a severe disability. An example of this would be that the first patient who presents with mild symptoms and is on a particular medication will be placed into group A (treatment group) the second patient who falls into the same category will be placed into group B (placebo group).

The treatment group was made up of 16 patients in total, 13 of which were female and 3 were male. The placebo group had 8 patients, with 5 of these being female and 3 being male.

Of the patients in the treatment group 37.5% were taking a DMARD, 37.5% were taking an NSAID and 25.0% were taking no medication. In the placebo group 25.0% of the patients were taking a DMARD, 37.5% were taking an NSAID and 37.5% were taking no medication.

The laser was applied in the manner recommended by Baxter (1994) and Kahn (1994). Group A received LLLT of the metacarpophalangeal (MCP)

joints and proximal interphalangeal (PIP) joints of the more severely affected hand. The open joint technique of application was utilised with the laser being applied in direct contact with the anterior, posterior, medial and lateral surfaces of the joints. The laser beam was directed at 90° (cosine law and law of reflection) to the surface so as to enhance penetration of the laser beam (Fischer, 1987).

Treatment Parameters

- ***Wavelength***: 675nm.
- ***Pulse repetition rate***: 5000Hz (Hall et al., 1994; Heussler et al., 1993).
- ***Time per spot***: 30 seconds (Heussler et al., 1993; Johannsen et al., 1994; Liggins, 2002).
- ***Joints treated***: Proximal interphalangeal (PIP) joints and metacarpophalangeal (MCP) joints (Hall et al. 1994; Liggins, 2002, Palmagren et al., 1989) of all 5 digits of the most severely affected hand.
- ***Laser technique***: Open joint technique – in contact with skin (Baxter, 1994; Boers et al., 1999; Hall et al., 1994; Johannsen et al., 1994; Kahn, 1994; Liggins, 2002)
- ***Treatment frequency***: 9 treatments over 3 consecutive weeks (3 treatments per week) (Jensen et al., 1987)

Whilst the patients in group A received LLLT, the patients in group B were treated with a laser that was not turned on. Group B's treatment was applied to the same joints, using the same technique and for the same number of treatments as the treatment group.

All participants received three treatments a week (e.g. on a Monday, a Wednesday and a Friday) for three weeks. They were assessed prior to the first treatment and then they were reassessed before the seventh treatment, again during the week following their final treatment and finally during the fourth week after their final treatment (a one month follow up).

Subjective measures consisted of the Numerical Rating Scale-101 (NRS-101), Disability of the Arm, Shoulder and Hand (DASH) Questionnaire and the duration of morning stiffness. Objective measures consisted of algometer readings.

Data Analysis:

Data analysis was done in SAS version 9.1 (SAS Institute Inc., Cary, NC). Baseline comparisons between the categorical baseline variables and the group to which the participant was assigned were done using Fisher's exact test. Continuous normally distributed baseline data were compared using the two sample t-test

Repeated measures analysis of variance (ANOVA) was used to analyse the treatment effect over time A p-value was then given for the time effect (whether there was a change in the readings over time) and for the treatment

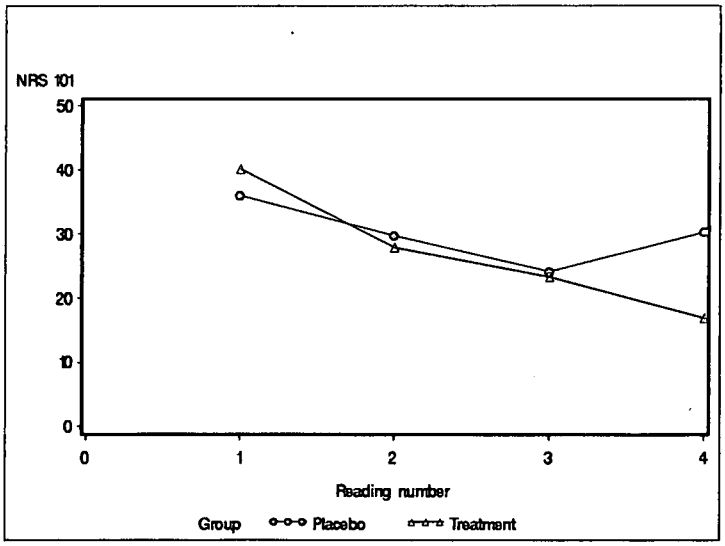
effect (whether there was a difference between the readings for the treatment and placebo groups). A visit by treatment interaction effect was also investigated.

In addition to these a paired t-test was done on the change from baseline to endpoint to determine whether there was any treatment difference between the two groups.

Results:

Table 1: p-values for NRS 101

Outcome	Effect	p-value
NRS 101	Visit	0.0034
	Visit by Treatment Interaction	0.2210
	Treatment	0.6624



Graph 1: Mean NRS score over time

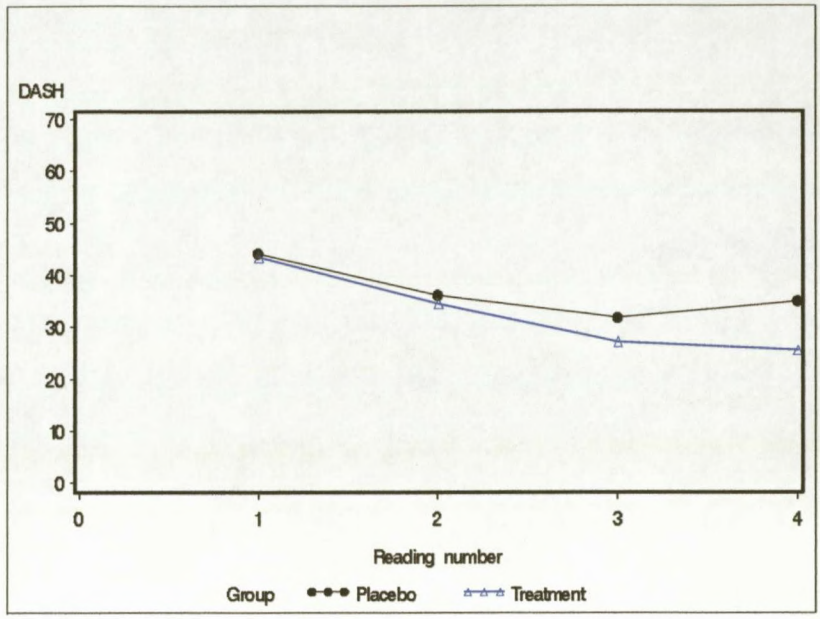
As evidenced by the above table and graphs, the NRS 101 values have shown a statistically significant visit effect (p = 0.0034), but no statistically significant visit by treatment interaction effect (p = 0.2210) or treatment effect (p = 0.6624). Both groups thus improved over time (shown by the statistically significant visit effect, p = 0.0034). This improvement did not, however, differ between the treatment and placebo groups (i.e. the placebo group improved as much as the treatment group).

The NRS 101 values improved in both groups for the first 3 readings, however the placebo groups' values then deteriorated again by the final reading whilst the treatment group values continued to improve over time.

The p-value for the difference between the baseline and final reading is 0.1093. This is not statistically significant, thus showing that by the end of the research protocol the patients had not achieved a statistically significant improvement in their pain.

Table 2: p-values for DASH Questionnaire

Outcome	**Effect**	**p-value**
DASH	Visit	0.0053
	Visit by Treatment Interaction	0.7440
	Treatment	0.6288

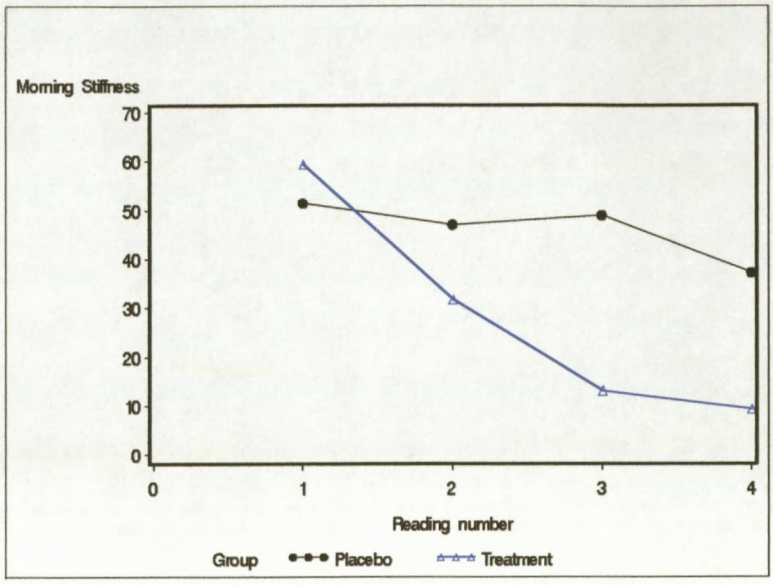


Graph 2: Mean DASH score over time

Both groups DASH scores improved over time (shown by the statistically significant visit effect). But since this improvement occurred in both the treatment and the placebo group, the improvement in the patient's daily functional ability caused by the LLLT was not found to be statistically significantly better than that caused by the placebo.

Table 3: p-values for Duration of Morning Stiffness

Outcome	**Effect**	**p-value**
Morning stiffness	Visit	0.00183
	Visit by Treatment Interaction	0.1691
	Treatment	0.3730



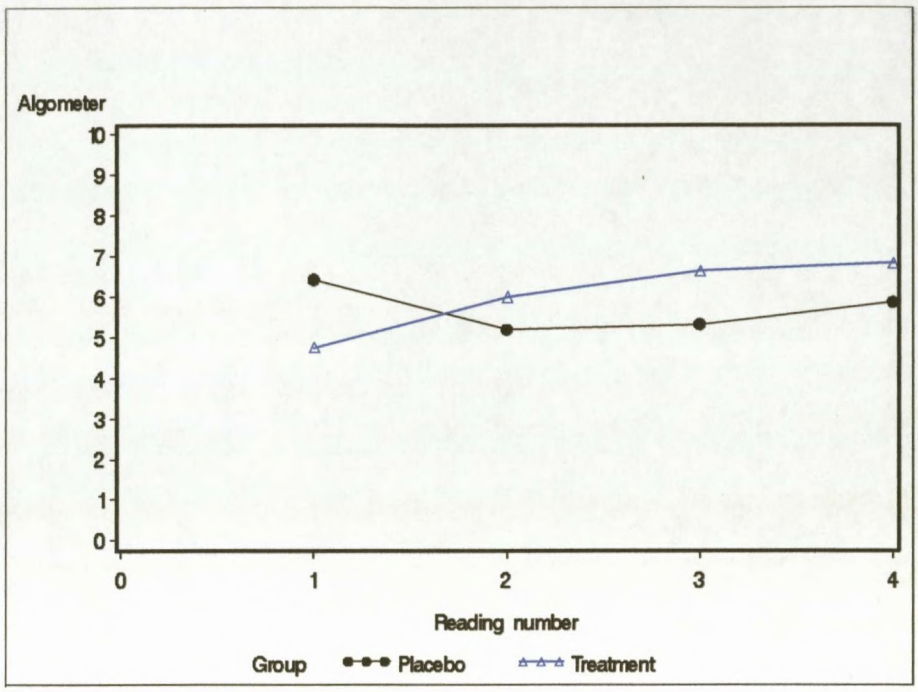
Graph 3: Mean morning stiffness over time

The above table and graphs indicate that although there was a change over time for both groups (which was more marked for the treatment group), it did not reach a level of statistical significance.

If only the difference between the baseline and the last value are analysed, the p-value for a difference between treatments is 0.1621, which is not statistically significant.

Table 4: p-values for Algometer Readings

Outcome	**Effect**	**p-value**
Algometer	Visit	0.1779
	Visit by Treatment Interaction	0.0010
	Treatment	0.7189



Graph 4: Mean algometer reading over time

As indicated by the above table and graphs, the algometer readings did not show a statistically significant difference in the visit effect or treatment effect. There was however a statistically significant visit by treatment interaction effect, meaning that at some visits the treatment effect was different than at some other visits.

If we only take the difference between baseline and the last value, the p-value for a difference between treatments is 0.0069, which is statistically significant.

Discussion and Conclusion:

The results of the study were found to suggest that there was no statistically significant difference in the treatment effect between the treatment and placebo groups The visit effect was statistically significant for most outcomes,

meaning that there was a significant improvement from one visit to the next but that neither the placebo nor the laser treatment was significantly more effective than the other.

The lack of a significant improvement in the readings for the treatment group relative to the placebo group may have been due to the fact that both groups were interacting with the researcher frequently over a short period of time while the treatments were taking place. As a result of this the patients may have been exhibiting the Hawthorne effect, whereby they showed improvement simply because they were getting special attention, and not necessarily because of the treatment they were receiving (Bailey, 1997). They would also have perceived that they were receiving treatment, they may have convinced themselves that they were improving.

However during the month after the 9 treatments, the placebo group may have found that they had not improved as much as they had first perceived and so during this period when they were not exposed to the researcher, their "improvement" regressed. In contrast the treatment group may have found that they had in fact improved, and thus during this 1 month period they may have continued to improve as a result of the treatment