"PROSPECTIVE RANDOMIZED CONTROLLED TRIAL ON THE EFFECT OF CALCITONIN IN SHOULDER ADHESIVE CAPSULITIS"

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ABSTRACT

Introduction: Adhesive Capsulitis is a painful musculoskeletal condition of the shoulder that affects many people. It is a common disease with a prevalence rate of 2–10 % in outpatients of orthopedic, rheumatologic, and physiotherapy clinics. The disease begins spontaneously and its gradual progress leads to shoulder pain and restriction in both active and passive movements of the glenohumeral joint. Although much work has been done to treat the disease, the results of nonoperative treatment of adhesive capsulitis are not satisfactory.

Very little literature is available on the effect of calcitonin in shoulder adhesive capsulitis, a proper randomized controlled trial is the need of the hour.

Aim: The aim of this study is to evaluate the effect of calcitonin in adhesive capsulitis and study its risk factors.

Methods: This randomized control clinical trial was conducted on 58 patients suffering from shoulder adhesive capsulitis. Patients diagnosed with adhesive capsulitis were divided into 2 groups, the intervention group and control group by computer randomization using Microsoft Randomizer version 2017.

The intervention group received intranasal calcitonin 200 units/day for 6 weeks along with Home based physiotherapy and NSAIDs.

The control group received only home based physiotherapy and NSAIDS.

The patients were evaluated pre- and post-treatment for shoulder pain and shoulder range of motion (ROM). Shoulder functional outcome (secondary outcome) was evaluated using Shoulder Pain and Disability Index questionnaire disability criteria.

Result: Out of 29 patients given intranasal calcitonin, 25 patients had relief of symptoms. Demographic characteristics and pre-treatment scores were improved in intervention group. In post treatment follow-up, shoulder pain, ROM, and the patients' functional scores were significantly improved in calcitonin group as compared to that of control group.

Conclusion : Intranasal calcitonin spray could be an additional safe alternative in shoulder adhesive capsulitis with regard to the efficiency in alleviating pain and improving functional outcome

Keywords : shoulder, adhesive capsulitis, calcitonin, frozen, physiotherapy, SPADI, ROM

LIST OF ABBREVIATIONS

AC	Adhesive capsulitis	**MMP**	Matrix Metalloproteinase
ANS	Autonomic Nervous System	**MPk**	Mud pack
ARR	Arthroscopic release and repair	**NSAIDs**	Non-Steroidal Anti-Inflammatory Drugs
aROM	Active Range of Motion	**NMDA**	N-Methyl-D-Aspartic Acid
AMPA	a-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid	***P***	Probability
DM	Diabetes Mellitus	**ROM**	Range of Motion
HMA	Hot mud application	**SD**	Standard Deviation
HTN	Hypertension	**SPSS**	Statistical Package for the Social Sciences
5-HT	5-Hydroxytryptamine	**SPADI**	Shoulder Pain and its Disability Index
MRI	Magnetic resonance imaging	**TGF-beta**	Transforming Growth Factor beta
VAS	Visual Analogue Scale	**PAS**	Periarthritis Shoulder
FS	Frozen Shoulder	**CRPS**	Complex Regional Pain Syndrome

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Adhesive Capsulitis is a painful musculoskeletal condition of the shoulder that affects many people (1). Duplay initially described frozen shoulder in 1872, calling it periarthritis. The inflammation of the subacromial and subdeltoid bursae was initially attributed to the major symptoms of progressive onset of shoulder stiffness, acute discomfort, especially at night, and restriction in active and passive range of motion of the shoulder (codman, 1911).

In 1945, Neviaser was the first to describe fibrosis and adhesions in the shoulder capsule in ten patients, coining the name "adhesive capsulitis" to describe the condition (J.S.Neviaer, 1945). (2).With these findings, observational studies have been undertaken, and it is widely acknowledged that the shoulder capsule is the cause of symptoms in periarthritis shoulder (3).

The musculoskeletal ailment adhesive capsulitis (AC), often known as frozen shoulder, is a common and painful condition.

The shoulder is a complicated joint with three bones, as well as several muscle groups, ligaments, and tendons. Inflammation of the joint is accompanied by stiffness, which severely limits the patient's range of motion and strength (5). Codman coined the term "frozen shoulder" to describe a disorder characterised by shoulder pain and discomfort that develops slowly and is centred around the deltoid insertion. The difficulty to sleep on the affected side is a common complaint among patients. There is also restricted glenohumeral elevation and external rotation, as well as unimpressive radiographic findings (6). The loss of range is multi-planar, with reduced passive external rotation and abduction being the most affected.

This condition is most typically reported in people between the ages of 40 and 75, is uncommon in youngsters, and is more common in women (7). Frozen Shoulder is thought to affect 3% to 5% of the general

population, and up to 20% of people with diabetes (8). Patients with adhesive capsulitis are more likely to have a pre-diabetic condition characterised by an abnormal fasting glucose or impaired glucose tolerance test (9).The loss of range is multi planar, with external rotation and abduction being the most affected restricted passive external rotation (10). Capsulitis is divided into four stages, which are unpleasant, freezing, frozen, and melting (11-13). Adhesive Capsulitis can cause shoulder immobility if it is accompanied by pain. Increased collagen length, fibrofatty infiltration into the capsule recess, ligament atrophy resulting in reduced stress absorption, collagen band bridging across recesses, random collagen production, and reformed sarcomere number in muscle tissue have all been linked to long-term immobilisation of a joint (14).

Adhesive Capsulitis is frequently diagnosed via exclusion. Clinically, it may resemble other shoulder diseases such as severe trauma, rotator cuff rupture, rotator cuff contusion, labral tear, bone contusion, subacromial bursitis, cervical or peripheral neuropathy early in the illness course. Shoulder stiffness can also be caused by a history of past surgical procedures. If there is no history of these illnesses and radiographs do not reveal osteoarthritis, the diagnosis of Adhesive Capsulitis can be made with certainty.

There are numerous intervention alternatives available and accessible today. Exercise therapy, electrotherapy, hydrotherapy, bupivacaine suprascapular nerve blocks using bupivacaine and methylprednisolone acetate in chronic shoulder pain, arthroscopic capsular release and repair, and bupivacaine suprascapular nerve blocks using bupivacaine and methylprednisolone acetate in chronic shoulder pain Complementary therapies like as physiotherapy and arthroscopic capsular distention are available to most patients (also called hydrodilation).
Although much work has been done to treat the disease, the results of nonoperative treatment of the adhesive capsulitis are not satisfactory.

Calcitonin is a polypeptide hormone produced by thyroid parafollicular cells. Calcitonin has an important role in the treatment of Complex Regional Pain Syndrome and other painful disorders such as rheumatoid

arthritis, fractures, spinal metastases, and bone tumours. The side effects of calcitonin inhaled through the nose are minimal and infrequent. Long-term calcitonin administration has been found to be safe and free of major adverse effects. Calcitonin may play a role in improving or preventing the advancement of symptoms of shoulder adhesive capsulitis, based on the reduction in pain in this diagnosis. The efficacy of calcitonin in shoulder adhesive capsulitis is little understood, and a proper randomised controlled trial is urgently needed.

Hence, the purpose of this study is to determine the effect of nasal calcitonin on clinical symptoms and progress of shoulder adhesive capsulitis

Aims & Objectives

Primary Objective:

The objective of this study is to evaluate the effect of calcitonin in adhesive capsulitis

Secondary Objective:

To study the risk factors of adhesive capsulitis

REVIEW OF LITERATURE

Anatomy of Shoulder joint(15) (FIG-1)

Consists of 3 bones and 4 articulations Three bones are

1.Clavicle

2.Scapula

3.Humerus

Four articulations

1. Acromioclavicular joint
2. Sternoernoclavicular joint
3. Glenohumeral joint
4. Scapulothoracic joint

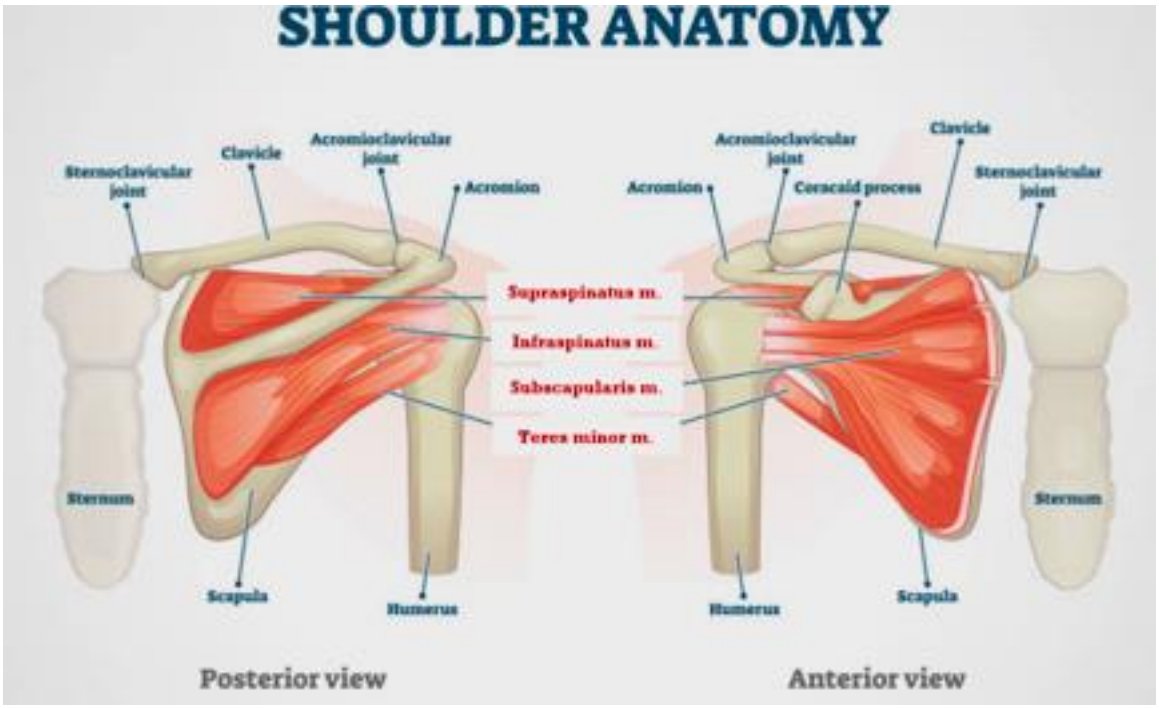

Fig 1 : Anatomy of the shoulder joint (15)

Stabilizers of shoulder joint

- **Static :** Bone geometry, Glenoid labrum , Joint Capsule, ligaments and Intra articular pressure
- **Dynamic** - Primary active stabilizers
- **Neuro muscular control**

Clavicle

It extends from the sternum (convex end) to the acromion(concave). Due to its S-shape, the lateral end undergoes more rotation during arm elevation compared to its medial end. The joint capsules of both the sternoclavicular and the acromioclavicular are further stabilized by ligaments.

Scapula

It's a flat bone and it acts as site of muscle attachment around the shoulder. It has 3 borders, 3 angles and 4 process. Its medial border is vertical and parallel to the spine. The inferior angle of scapula is at the level of spinous process of D7.

The four processes of scapula are coracoid process, acromion, spinous process and glenoid fossa (articular process).

It is convex in the dorsal aspect. Its divided into two fossae by the spinous process: Supraspinous fossa and Infraspinous fossa.

Humerus

The articular area of the head of humerus, which is retroverted and medial, is separated from the greater and lesser tuberosities by its anatomical neck.

Glenoid cavity(16): (Fig 2)

Glenoid fossa is at the lateral end of the scapula. It is pear shaped, having an inferior surface which exceeds the superior surface by 20%. Its alignment is anterolateral with a cranial tilt. It is 25% the size of the head of humerus. This is why, Shoulder joint enjoys mobility at the cost of stability.

Glenoid labrum (Fig 2)

Its fibro cartilaginous rim located along the glenoid fossa s border. It attaches to peripheral margin of glenoid cavity except above. It deepens the glenoid fossa and forms pliable cushion for ball to roll. It gives attachment to glenohumeral ligaments

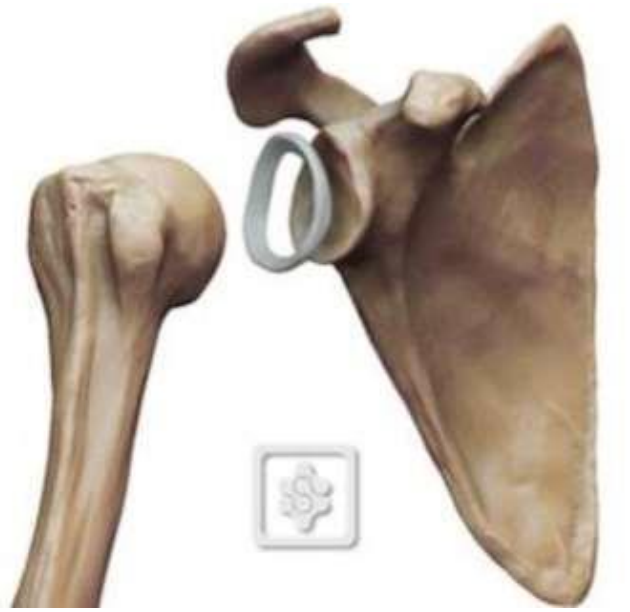

Fig 2 : Glenoid Labrum and Glenoid Cavity (16)

Gleno-humeral ligaments (17)(Fig 3)

They are located in front of the joint and are construed as the capsule's thickened areas.

- Superior gleno-humeral ligament (SGHL)
- Middle gleno- humeral ligament (MGHL)
- Inferior gleno- humeral ligament (IGHL)

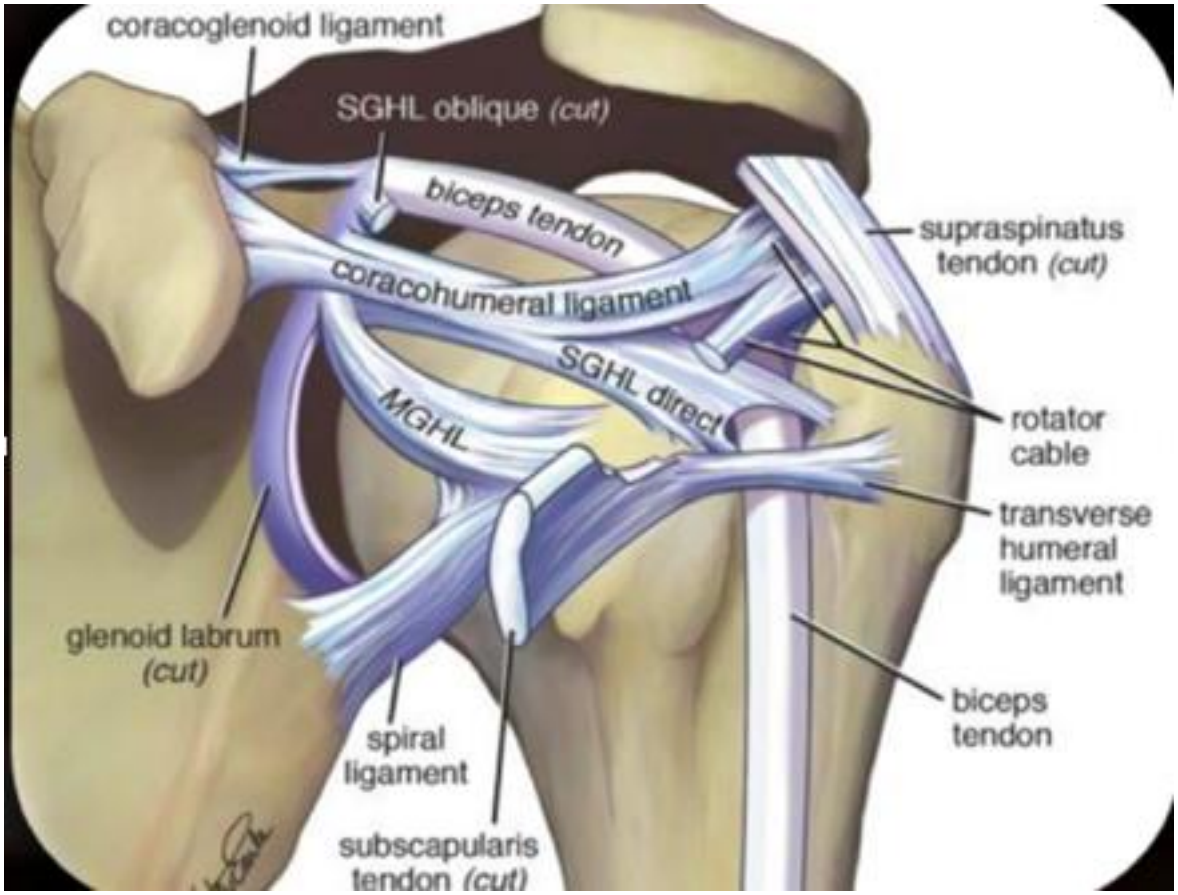

Fig 3 : Gleno-humeral ligaments (17)

SGHL -extends from the glenoid labrum's upper part and the coracoid base to the humeral head, precisely in between the lesser tuberosity's superior part and the anatomical neck. Along with coraco humeral and supraspinatus, it prevents the downward displacement of humeral head.

MGHL- extends from the glenoid fossa's anterior margin below SGHL attachment and passes to the humeral neck. It stabilizes the joint anteriorly in the mid abduction.

IGHL- extends from anterior-posterior margins of the lower glenoid labrum and forms an inferior pouch. the thick anterosuperior part is called the superior band. The inferior part is named the axillary pouch. The lower component of the IGHL offers buttress -like support for the joint's anterior and inferior parts. This segment stabilizes the joint in the upper abduction ranges, while negating subluxation and dislocation anteriorly

Sterno clavicular joint (18)Fig 4)

The SC articulation consists of two saddle-shaped surfaces one at the sternal or medial end the clavicle and one at the notch formed by the manubrium of the sternum and first costal cartilage.

Ligaments of sternoclavicular joint:

- Capsular ligaments
- Sternoclavicular ligaments – anterior & posterior
- Interclavicular ligaments
- Costo clavicular ligaments
- Articular disc

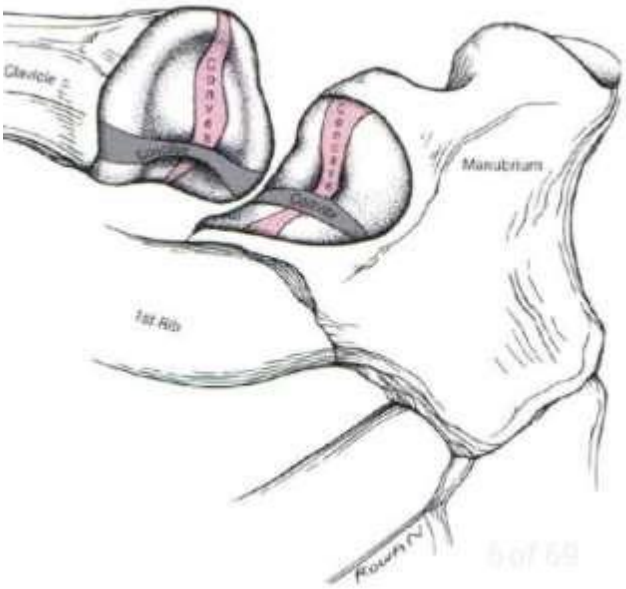

Fig 4 : Sterno-clavicular joint (18)

Articular disc (19)(Fig 5)

It is a fibrocartilaginous disc to increase the congruency b/w incongruent articular surface. It diagonally transects the SC joint space and divides the joint into 2 separate cavities. It is considered part of the manubrium in elevation /depression and thus the upper attachment of the disc serves as pivot point and the disc acts as the part of the clavicle. (19)

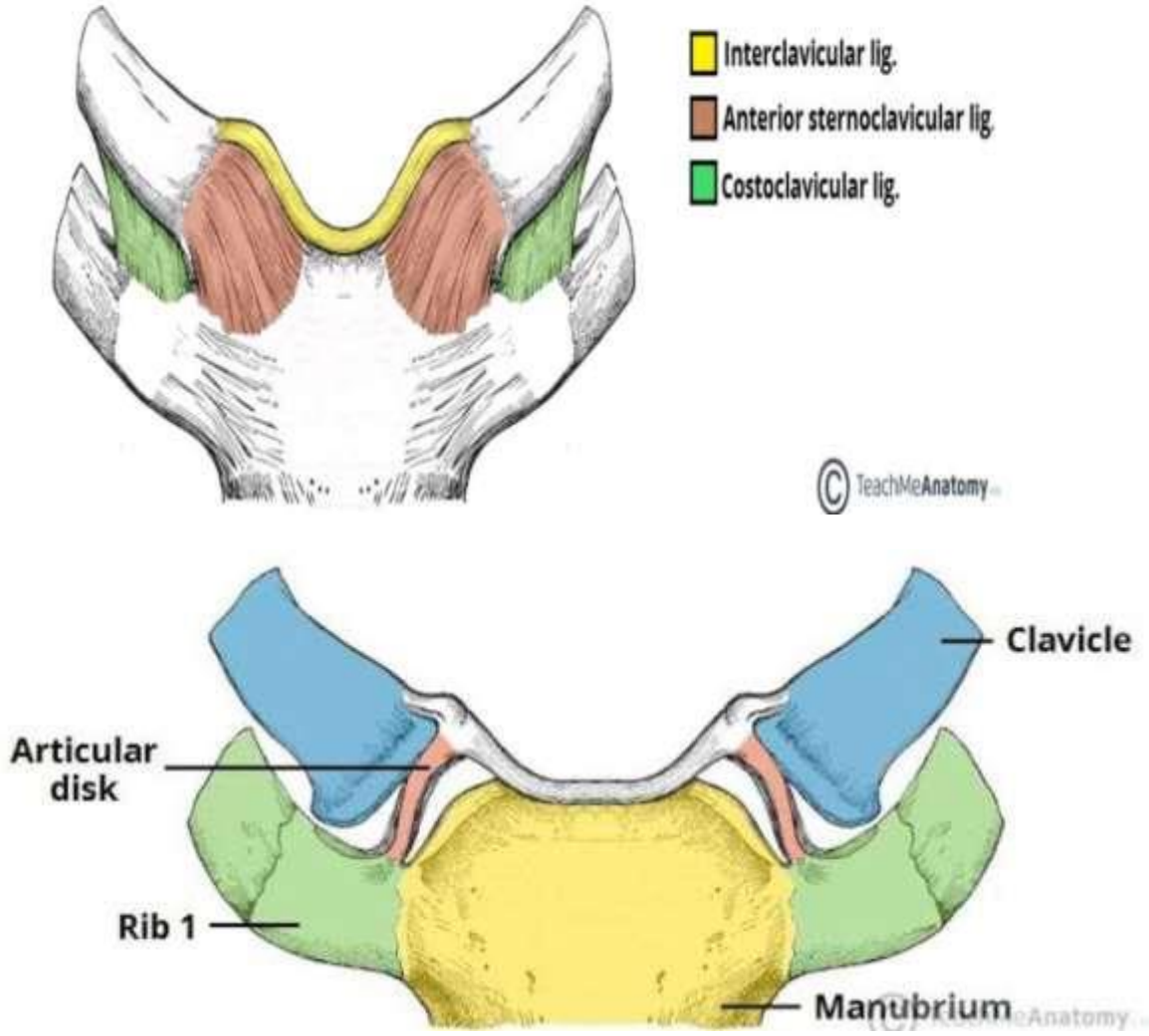

Fig 5 : Articular Disk (19)

Acromio clavicular joint (Fig 6)

It allows the scapula additional range of rotation on the thorax and allow for adjustments of the scapula outside the initial plane of the scapula in order to follow the changing shape of the thorax as arm movement occur. In addition, the joint allows transmission of forces from the upper extremity to the clavicle.

Ligaments of acromio-clavicular joint (21):

- Fibrous capsule
- Acromio-clavicular ligaments
- Coraco-clavicular ligaments
- Conoid part -oriented vertically, resists superior & inferior forces
- Trapezoid part -oriented horizontally
- Coraco-acromial ligament

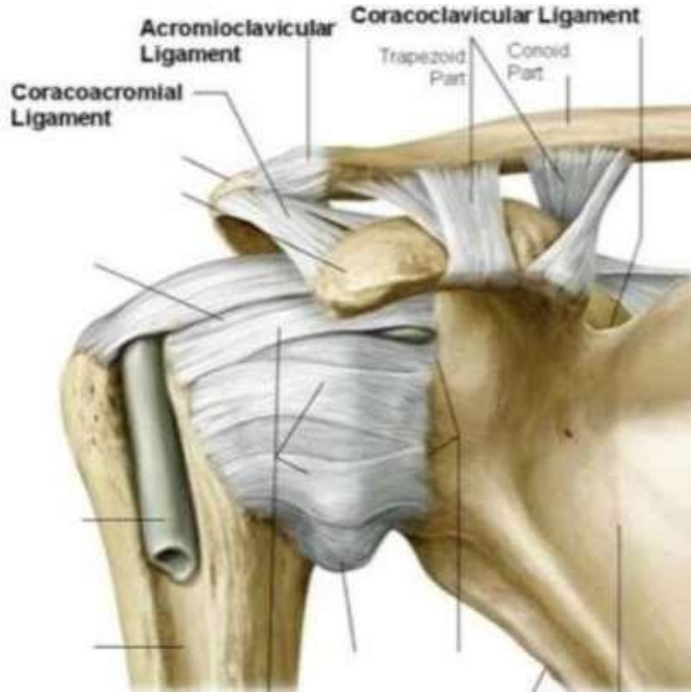

Fig 6 : Acromio-clavicular joint (21)

Glenohumeral joint

It is a ball -socket type of joint. The articulating surface of the head of humerus is spherical, with an arc of 160˚of articular cartilage.

The humeral articular surface has a radius of 25mm. The glenoid articular surface's curvature radius is 2-3mm larger than that of head of humerus.

The neck shaft angle is 45˚. Humeral head is retroverted 30-40˚and glenoid is 2˚of anteversion to 7˚of retroversion. (22) (Fig 7)

Ligaments of Glenohumeral joint:

- Fibrous capsule
- Glenohumeral ligaments
- Coraco humeral ligament
- Transverse humeral ligament

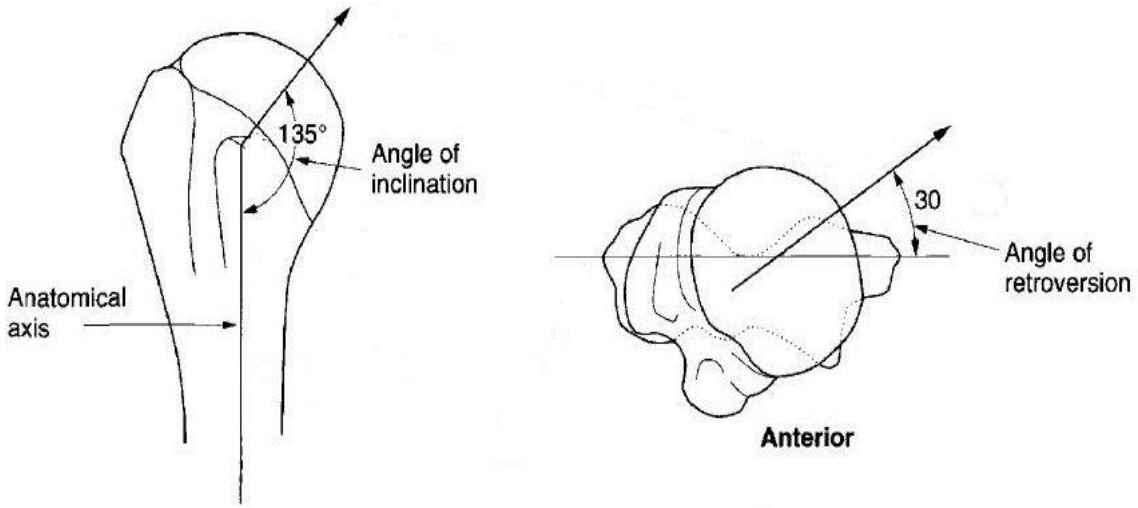

Fig 7: Angles of inclination of Humerus (22)

Scapulothoracic joint (Fig 8)

It is not a true anatomic joint. The functional Scapulothoracic joint is part of a true closed chain with the Acromio Clavicular and Sterno Clavicular joint and the thorax. Example, When the arm is abducted, scapula undergoes upward rotation, external rotation and posterior tipping (all movements in combination)

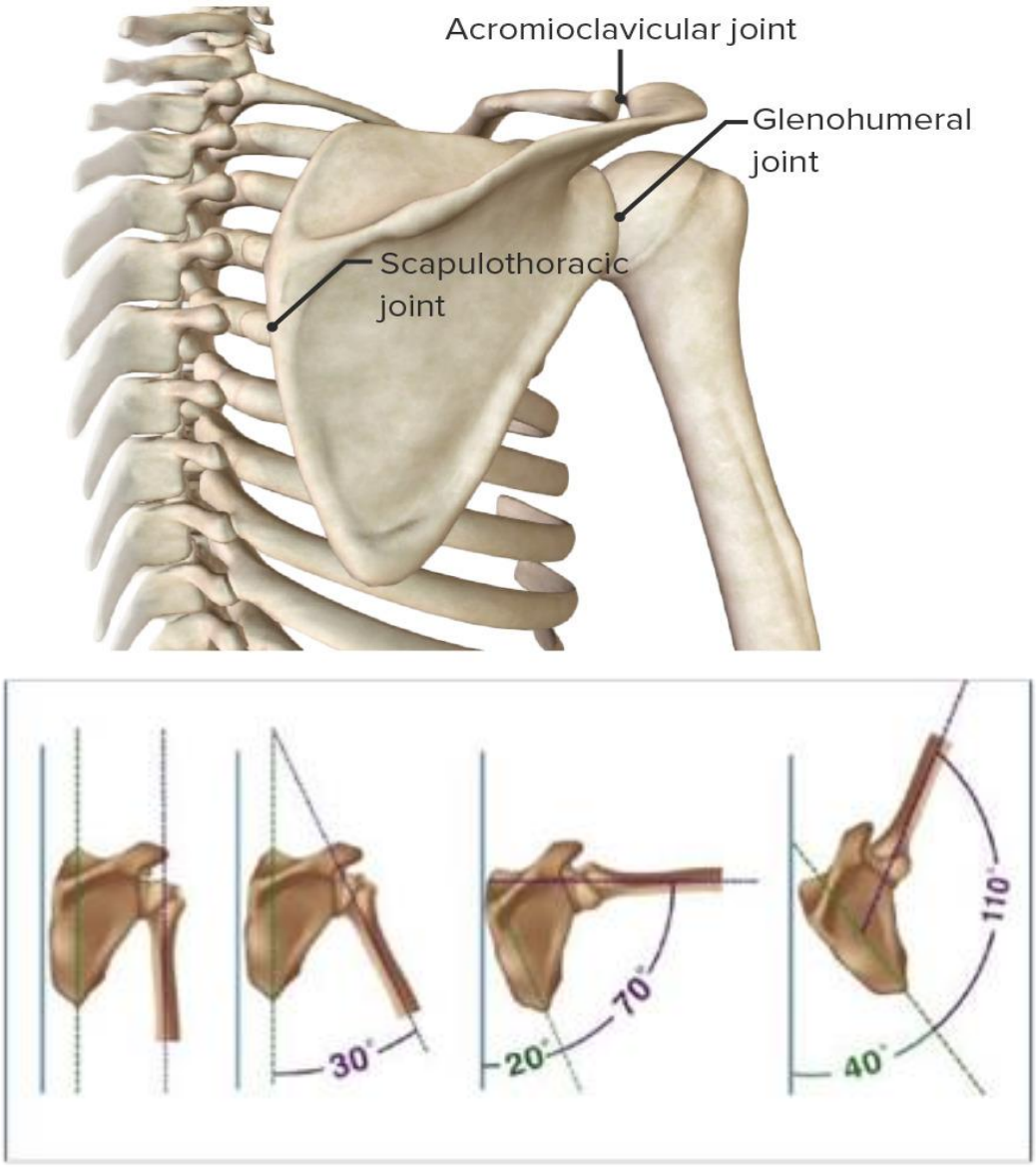

Fig 8: Scapulothoracic joint (24)

Shoulder movements & the muscles responsible for range of motion (Fig 9)(24)

1. Flexion

Pectoralis major, Biceps brachi and Anterior Deltoid

2. Extension

Posterior Deltoid, Teres major , Latissimus dorsi

3. Abductors

Supraspinatus, Deltoid, Trapezius & Serratus anterior

4. Adductors

Subscapularis, Infraspinatus, Teres minor & Major and Latissimus dorsi

5. Internal rotation

Subscapularis, Latissimus dorsi, Anterior fibres of deltoid, Pectoralis major & Teres major

6. External rotation

Infraspinatus, Teres minor, Posterior fibres of deltoid

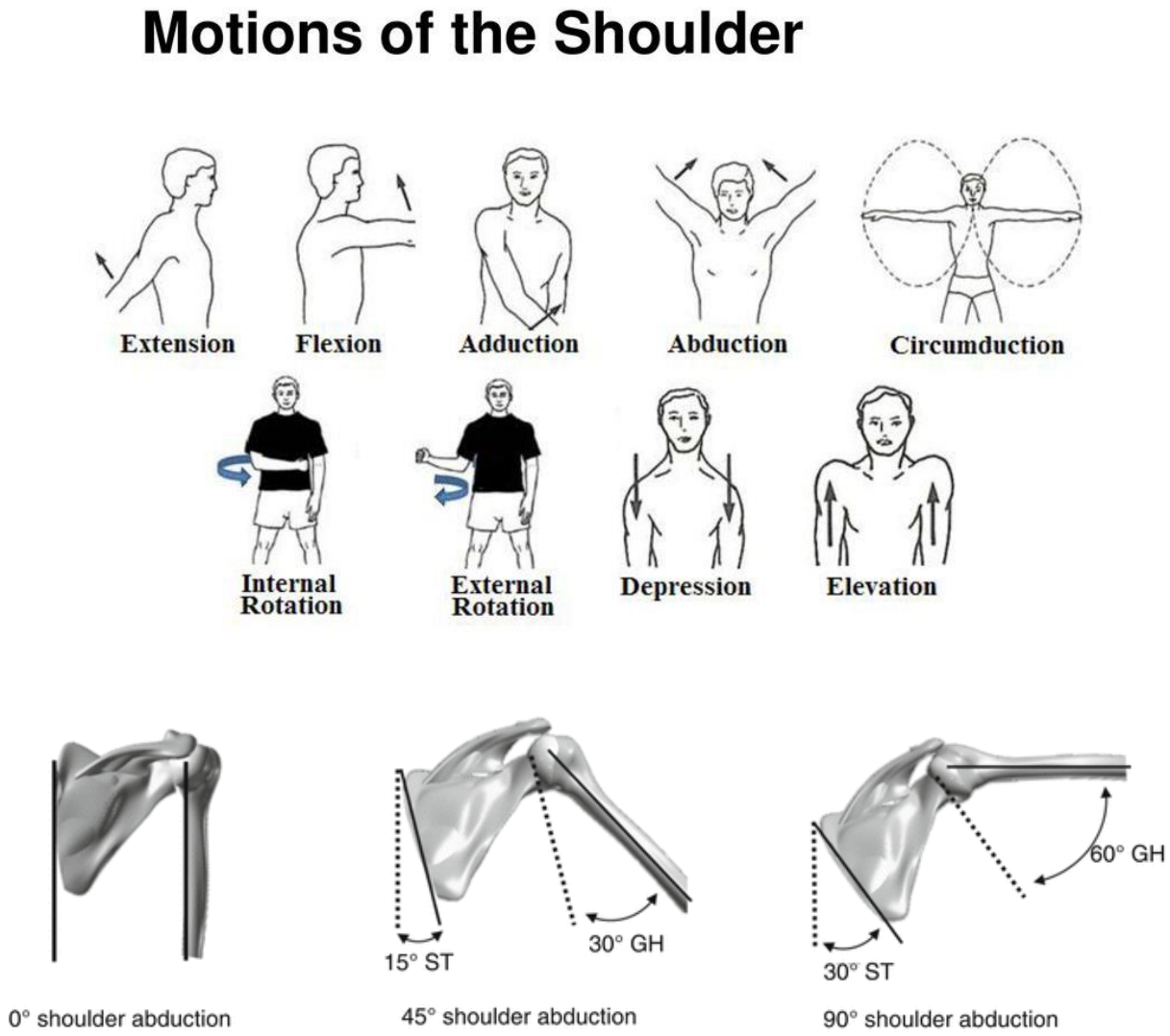

Fig 9 : Shoulder movements & the muscles responsible for range of motion (25)

Vascular supply of the shoulder joint : (Fig 10)

Anterior & posterior circumflex humeral, suprascapular & circumflex scapular vessels (26)

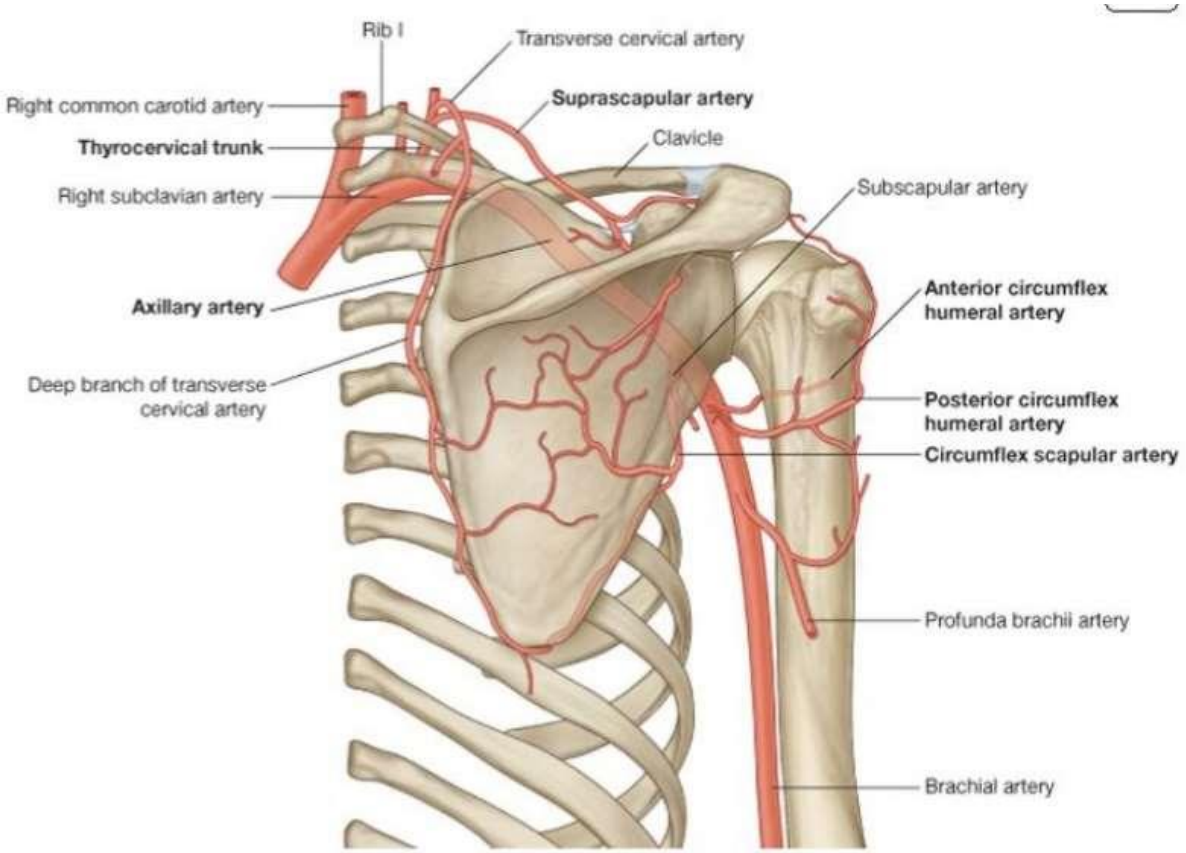

Fig 10: Vascular supply (26)

Nerve supply of the shoulder joint : (Fig 11)

The capsule is supplied by the suprascapular nerve (posterior & superior branches) and axillary nerve (anteroinferior) (27)

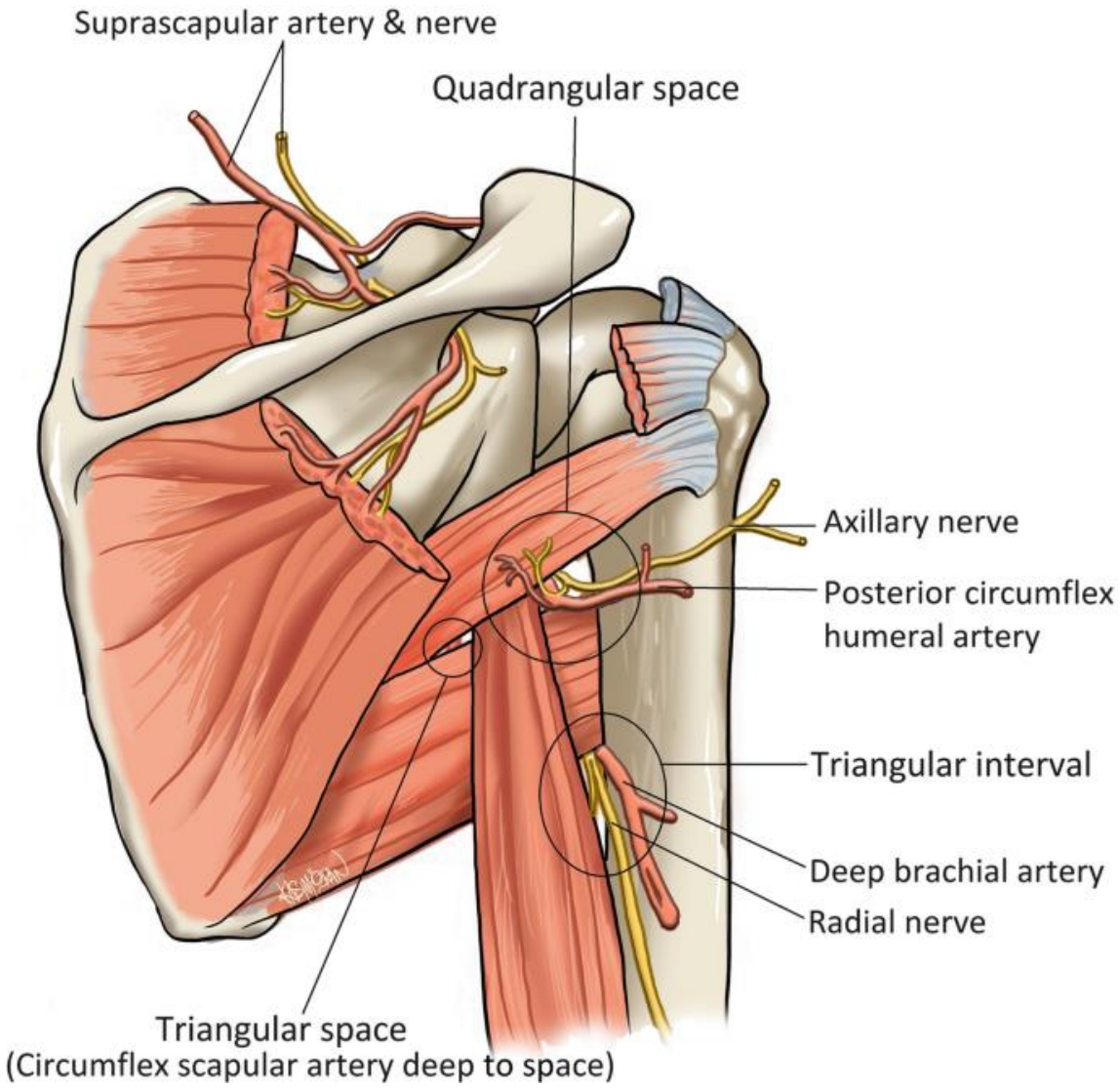

Fig 11 : Nerve supply (27)

ROTATOR CUFF (28) (Table 1) (Fig 12)

The Rotator Cuff (RC) is a common name for the group of 4 distinct muscles and their tendons, which provide strength and stability during motion to the shoulder complex. They are also referred to as the SITS muscle, with reference to the first letter of their names The muscles arise from the scapula and connect to the head of the humerus, forming a cuff around the glenohumeral (GH) joint.(28)

Supraspinatus muscle	Origin: supraspinatus fossa of scapula Insertion: greater tubercle of humerus Innervation: suprascapular nerve (c4, c6) Function: initiation of abduction of arm to 15° at glenohumeral joint; stabilization of humeral head in glenoid cavity.
Infraspinatus muscle	Origin: infraspinatus fossa of scapula Insertion: greater tubercle of humerus Innervation: suprascapular nerve (C5, C6) Function: external rotation of arm at glenohumeral joint; stabilization of the humeral head in glenoid cavity.
Teres minor muscle	Origin: lateral border of scapula Insertion: greater tubercle of humerus Innervation: axillary nerve (C5, C6) Function: external rotation and adduction of arm at glenohumeral joint; stabilization of the humeral head in glenoid cavity.
Subscapularis muscle	Origin: medial two-third of the subscapular fossa Insertion: lesser tubercle of the humerus Innervation: upper and lower subscapular nerves (C5, C7) Function: internal rotation of arm; stabilization of humeral head in glenoid cavity.

Table 1 : Rotator cuff muscles

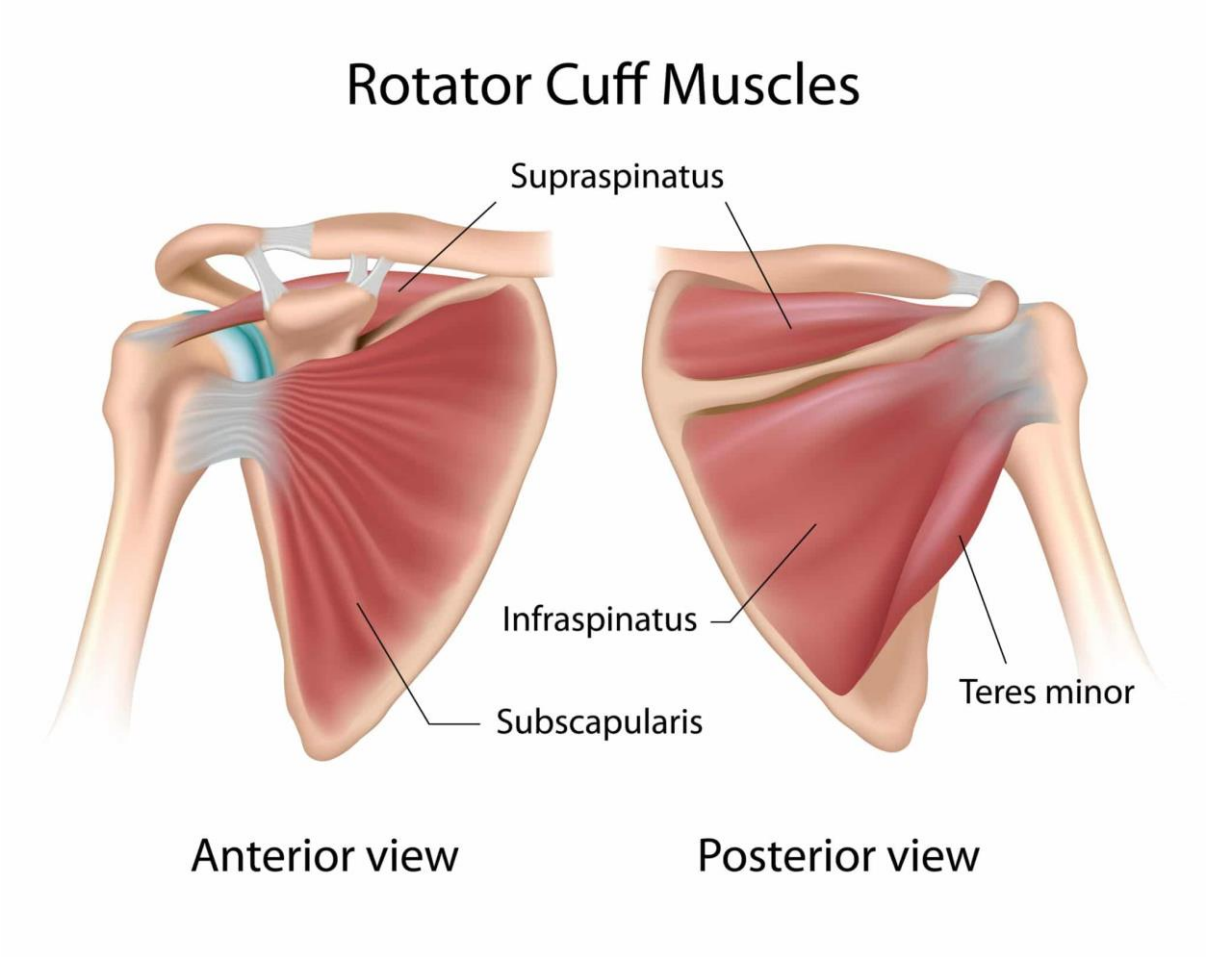

Fig 12 : Rotator cuff muscles (28)

ROTATOR CUFF INTERVAL: (Fig 13)

The rotator cuff interval is a triangular space between the tendons of subscapularis, supraspinatus and the base of coracoid process.

It is roofed by the rotator interval capsule , which is principally made up of the coracohumeral ligament . It contains the tendon of long head of biceps and the superior glenohumeral ligament

The combination of the coraco humeral ligament and superior gleno humeral ligament have a complex relationship to the long Head of biceps tendon, acting together to hold the LHB from subluxing or dislocating anteriorly.

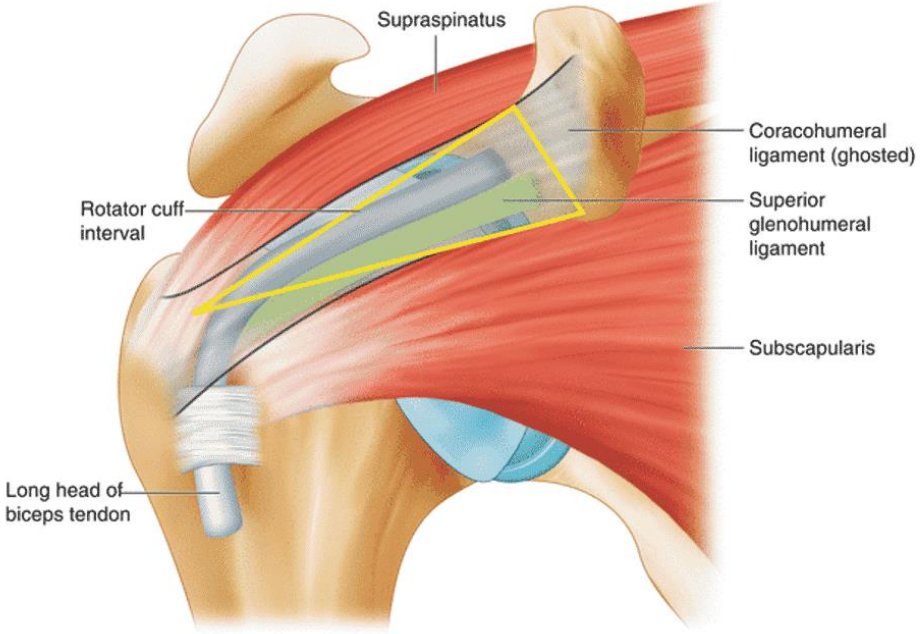

Fig 13 : Rotator cuff interval (29)

An Overview of Adhesive Capsulitis (AC)

Frozen shoulder is a musculoskeletal disorder with self-limiting condition in shoulder joint. Patients typically present with a history of progressive painful restriction in range of movement of the shoulder joint. They reveal a capsular pattern of limitation with external rotation and being the most affected followed by abduction in the level of the scapula and then finally flexion. In 1934 Codman described a diagnostic criteria which involves of idiopathic onset, painful restriction of all gleno-humeral movements with limitation of flexion and external rotation without any radiological changes.

Adhesive capsulitis associated with pain can cause an immobilization of a shoulder. Prolonged immobilization of a joint has been shown to cause several detrimental pathophysiologic findings.

Epidemiology

Frozen shoulder is approximately 2-3 percent in the general population (30). It is peaks among 40-65 years of age and infrequent in children. but women are more frequently affected than men, but there is no known genetic or racial preference.it is commonly affect in persons with insulin-dependent and non-insulin-dependent diabetes, and in those with pre-diabetes (glucose intolerance).

Persons with a history of Frozen Shoulder are at increased risk of developing the condition on the contralateral side. Recurrence side is also possible, especially in patients with diabetes.

Adhesive Capsulitis and Diabetes Mellitus (31)

Studies have presented that correspondence between Adhesive Capsulitis and diabetes mellitus (DM), with the incidence of two to four times higher when matched with general population. It affects about 20% of people with DM and has been described as the most disabling of the common musculoskeletal manifestations of diabetes. The prevalence of diabetes in patients with adhesive capsulitis was 71.5% DM increases the risk of microvascular complications and believed to play a role in the developed of musculoskeletal complications (31).

History of Adhesive Capsulitis

Reeves, in a prospective study had a follow up for 5-10 years with 41 patients, out of them he have observed that 39% recovered completely, 54% had clinical limitation without functional changes, and 7% had functional limitation (17).Shaffer et al showed that 50% of his 61 patients with adhesive capsulitis had certain degree of pain and stiffness on an average of seven years after onset of the disease (32).

Phase of Clinical Presentation

Neviaser et al (33) and Hannafin et al (34) said that 4 stages in Frozen Shoulder, which have been correlated with clinical examination and histological features.

1. Painful Stage
2. Freezing Stage
3. Frozen Stage
4. Thawing Stage

Painful Stage

First stages in Frozen Shoulder is the painful stage, which is characterised by a progressive beginning of pain. It continues less than 3 months on the insertion of deltoid muscles and in ability to sleep on the affected side. Patients may report a mild restriction of ROM which perpetually resolves with the advise of local anaesthesia (35). Arthroscopic perspectives demonstrates a hypertrophic, vascularized synovitis without grips or capsular contracture.

Freezing Stage

The second stage is also classified "solidifying stage" symptoms proceed for 3 to 9 months and are described by increasing of nocturnal pain while resting on the influenced side, also a significant loss of both active and passive ROM can be taken noticed. Arthroscopic view demonstrates a thickening of perivascular synovitis (36). Histologically demonstrates perivascular and sub synovial scar development with deposition of disordered collagen fibrils with a hypercellular appearance, however no any inflammatory infiltration.

Frozen Phase

In frozen (or) "solidified stage (36) symptoms persists 9 to 14 months, the shoulder firmness is transcendent and pain may persevere towards the end of movement or during the sleep on the affected side. Arthroscopic examinations exhibit loss of axillary recess, patchy synovial thickening and biopsy shows dense hypercellular collagenous tissue.

Thawing Phase

The last stage is thawing or "defrosting stage". It is described by minimal pain and a gradual progression of ROM because of capsular remodeling. This stage happen somewhere in the range of 15 and two years (36). Arthroscopic and histological correspondence has not been explored.

Physical Examination

Chronic Adhesive Capsulitis patients may lose characteristic swing of the arm that happens while walking. Shoulder support muscles atrophy can be taken note. Debilitated movement in the glenohumeral joint may result with irregular scapular development with active forward flexion of the affected shoulder. Physical examination of a patient with Frozen can be uneasiness and require brief rest or delicate release their arm to demonsrate the moves. Palpation may yield dubious, diffuse tenderness over the anterior and posterior shoulder. Central tenderness over unequivocal structure is uncommon and its essence proposes differential determination or attendant pathologies, for example, rotator cuff or biceps tendinopathy.

Frozen Shoulder susceptibility can be raised when flexion, abduction, and external rotation were confined. Examination of the two shoulders can uncover the precise survey shortages of the influenced side. The patient should initially be solicited to actively test the breaking points from movement; if loss of movement is watched, the doctor may assist passively, with scapular adjustment to ensure a precise estimation of movement.

Clinical Presentation

Frozen shoulder is a clinical conclusion. The three all marks of solidified shoulder are active shoulder firmness, severe pain (particularly around night time) that results inability to sleep on the affected side and a close total loss of uninvolved and active external rotation of the shoulder. Appropriate history-taking incorporates the onset and duration of symptom, site, function and preceding truama. Past therapeutic and careful history is significant and relevant and should be obtained. On inspection, mild diffuse atrophy of the deltoid and supraspinatus in long standing cases is usually observed. The arm may be adducted and

internally rotated. Tenderness would be positive on palpation of the glenohumeral joint. Both active and passive range of motion are affected, especially that of abduction and external rotation. Movement in the thoracoscapular joint, which may aid abduction, should be noticed.

The hallmark of Adhesive Capsulitis is decreased range of motion and shoulder pain there often idiopathic cause or trigger. The pain is often described as a poorly localized and deep ache. If the pain is localized, it is usually in the area of the anterior or posterior capsule. It may radiate to the biceps with progressive pain and stiffness when performing flexion, abduction and external rotation. Weakness is often correlated to pain or concomitant tendinopathy. Crepitus may be present on the involved side. Like other shoulder conditions pain may be impair sleep.

Pathogenesis of Adhesive Capsulitis (37) (Fig 14)

Neviaser noted that Frozen Shoulder condition was actually located in the capsule of the shoulder joint and therefore called adhesive capsulitis. Therefore the pathophysiological process is believed to involve synovial inflammation and fibrosis of the shoulder joint capsule , with microscopic examination of the tissue one will find the majority of the cells to be fibroblasts with some mast cells also present. Cytokines such as transforming growth factor β and platelet –derived growth factor may contribute to the inflammatory process. Although the glenohumeral joint, synovial capsule is involved, much of the disease also involves structures outside the glenohumeral joint. These structures can include the coracohumeral ligament, rotator interval, subscapularis, musculotendinous and the subacromial bursa (37).

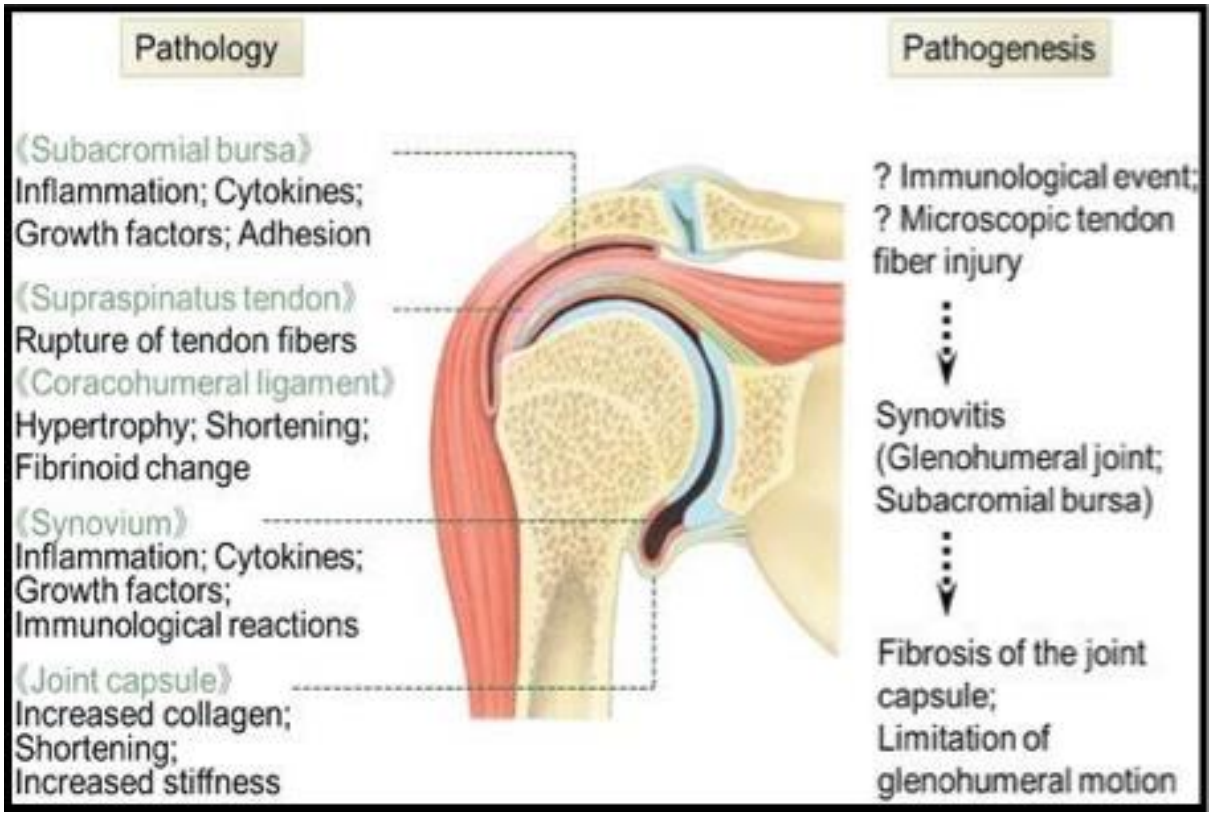

Figure 14: Pathogenesis of Adhesive Capsulitis (38)

Adhesive Capsulitis includes both synovial inflammation and capsular fibrosis. Characteristically pain with restriction, it is most likely to have inflammation with fibrosis. Cytokines such as tumour necrosis factor-alpha (TNF-alpha) and Interleukins (ILs) also cause synovitis in both the glenohumeral joint and subacromial bursa, however matrix- bound transforming growth factor beta (TGF-beta) may act as a persistent stimulus and resulting in capsular fibrosis . Another likely initiator of synovitis is degeneration or injury of the rotator cuff tendon. Tendon injury may trigger induction of inflammatory mediators or fibrotic cytokines in the shoulder joint, where as partial rotator cuff tear may cause joint contracture(37)

Capsule of Glenohumeral Joint (39) (Fig 15)

The fibrous membrane of the joint capsule is thickened: antero superiorly in three locations to form superior, middle, and inferior glenohumeral ligaments, which pass from the superomedial margin of the glenoid cavity to the lesser tubercle and inferiorly related anatomical neck of the humerus superiorly between the base of the coracoid process and the greater tubercle of the humerus (the coracohumeral ligament); between the greater and lesser tubercles of the humerus (transverse humeral ligament)-this holds the tendon of the long head of the biceps bronchi muscle in the intertubercular sulcus . Joint stability is provided by surrounding muscle tendons and a skeletal arch formed superiorly by the coracoid process and acromion and the coraco- acromial ligament .

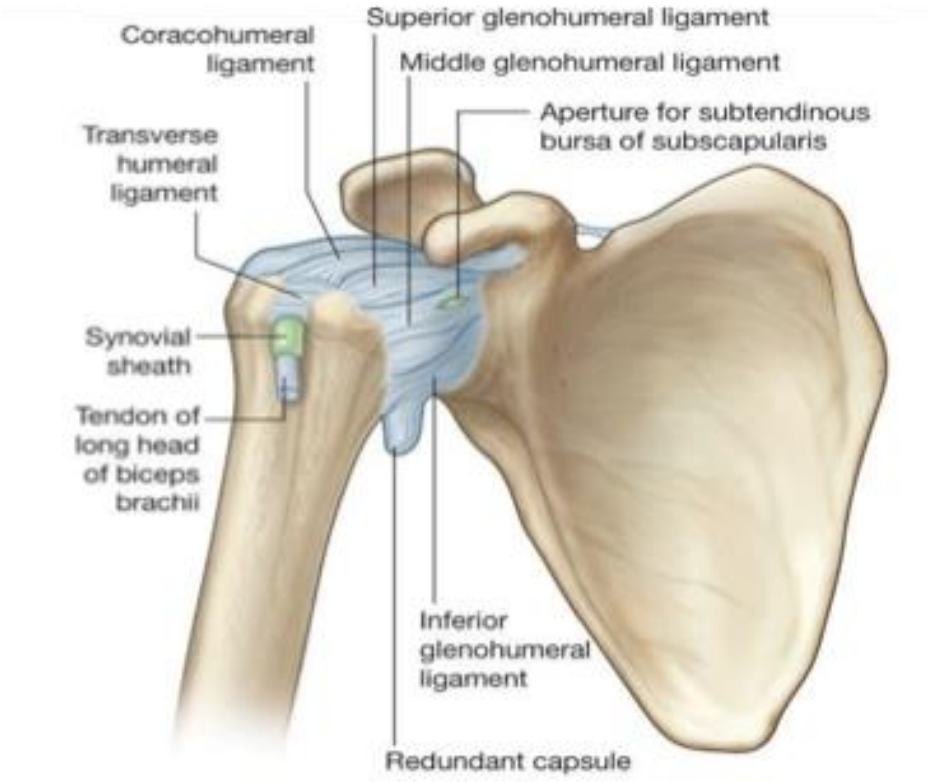

Figure 15: Capsule of glenohumeral joint (39)

Differential Diagnosis

Diagnosis of Adhesive Capsulitis is generally clinical. Other conditions that would be considered in a patient who presents with a stiffness, painful shoulder include acromio clavicular arthropathy, autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis), cervical disc degeneration, biceps tendinopathy, glenohumeral osteoarthritis, neoplasm, rotator cuff tendinopathy or tear (with or without impingement), sub acromial and subdeltoid bursitis. Frozen Shoulder in the presence of related conditions is most appropriately defined as painful shoulder syndrome.

Diagnostic Testing

Laboratory

Blood glucose parameters should be the priority of the doctors as a result of high prevalence of diabetes and pre-diabetes in patients with Frozen Shoulder. Extra serological tests are normally not shown, however may be performed that they are suspecting any immune system or infectious conditions. C-reactive protein and erythrocyte sedimentation rate levels may be raised in patients with Frozen Shoulder, however these tests are not specific or sensitive.

Imaging

Radiographic evaluation: (40)

1. X ray of the shoulder is usually normal.
2. Arthrogram (Fig 16) of the shoulder is useful in showing the available volume of the joint cavity.

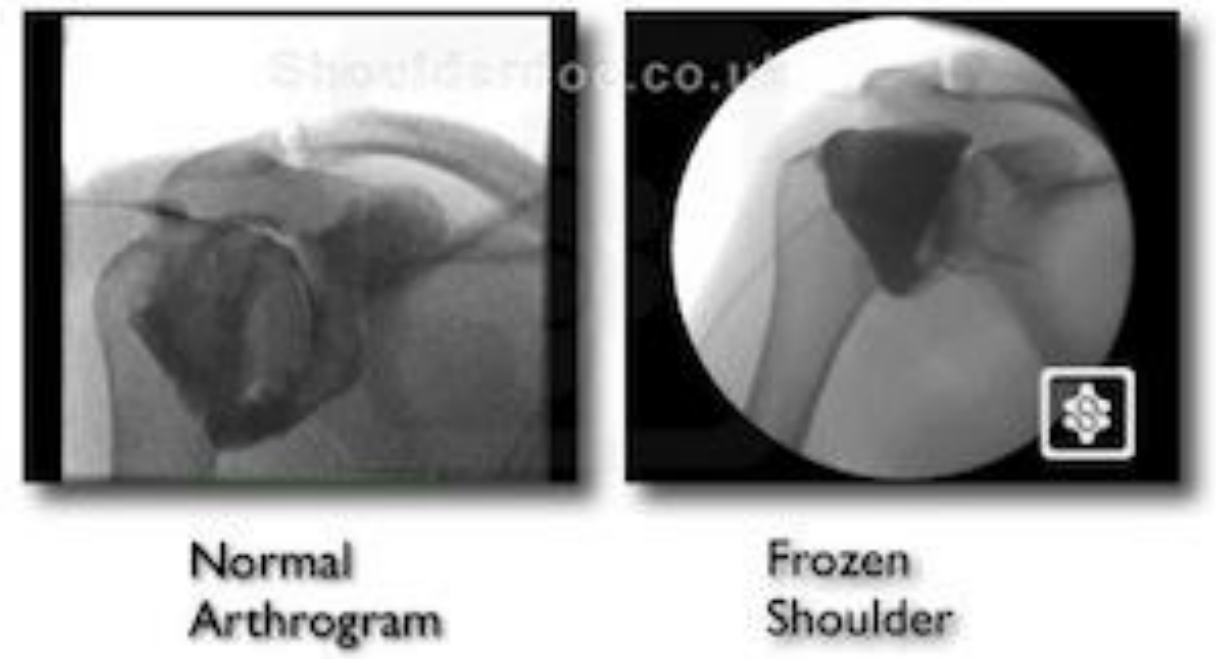

Fig 16 : Arthrogram of a frozen shoulder (40)

3. MRI of the shoulder joint (Fig 17)

- It is the gold standard imaging for diagnosing adhesive capsulitis (41)
- The normal inferior glenohumeral ligament measures <4mm and is best seen on coronal oblique images at the mid glenoid level. In adhesive capsulitis, the axillary recess may show thickening up to 1.3 cm or more; the joint capsule is also thickened
- Classical " subcoracoid triangle sign is seen" in sagittal oblique T1 weighted images

Fig 17 : MRI of shoulder showing adhesive capsulitis(41)

Authoritative finding of Frozen Shoulder can be obtained distinctly through direct surgical observation. All things considered, this isn't generally essential. Other imaging strategies can be utilized to supplement the previous history and physical examination (42).

The glenohumeral joint capsule is comprising of soft tissue; consequently plain radiography may not be useful. it may, radiography can distinguish other shoulder pathologies. X-beams can be helpful to evaluate for pathologic fracture, avascular necrosis, calcific rotator cuff, progressed glenohumeral joint pain, and biceps tendinopathy.

Magnetic resonance imaging (MRI) isn't diagnostic for PAS. Capsular thickening can be seen on MRI, it may likewise accommodating in distinguishing different conditions, for example, subacromial bursitis and rotator cuff tendinopathy (43).

Treatment

Many treatments have been advocated for frozen shoulder. The existence of so many different treatments, each with its own group of enthusiastic supporters, suggests that no single treatment is unequivocally superior to others. The fundamental goal of treatment is to restore and maintain function.

1. **Anti-inflammatories**

Employments of hostile to inflammatories or corticosteroids are the significant in the treatment of frozen shoulder. Non-steroidal anti inflammatory drugs (NSAIDs) may be utilized in brief pain relief .

No evidence has demonstrated to show that NSAIDs change the visualization of frozen shoulder. Be that as it may, NSAID's are included in the activity of hostile to irritation as well as creating pain relieving impact. So it very well may be sensible prime decision for frozen shoulder.

In addition, No comparative study has done on oral corticosteroids with placebo treatment or natural history of the frozen shoulder. Most studies have demonstrated that corticosteroids may reduce pain than recovery or placebo treatment however their results are not maintained long term

2. **Intra Articular Steroid injection (Fig 18) (44)**

Steroid injection is one of the most important medications for Frozen Shoulder. Various Cochrane surveys have inferred that inevitable area of a subacromial or visually impaired glenohumeral injection is profoundly factor (44). Ongoing Cochrane audit groups the outcome from twenty six heterogenous examinations and presumes that there is a little transient advantage to steroid injection alone for frozen shoulder however the evidence is uncertain.

Albeit high quality RCT of corticosteroid injection for treatment of frozen shoulder have not been done, accessibility of some evidence on intra-articular injections demonstrates that having transient advantage of their utilization. Negligible difficulties of utilizing this intrusive system like subacromial infusion or glenohumeral injections may be considered. Impediment of administrating injection is visually impaired with incorrectness of 60%. Advance clinical practice may have more noteworthy precision. This limitation can be overwhelmed by utilization of imaging strategies, for example, ultrasound guided joint injection.

Fig 18 : Intra articular injection of steroids (45)

3. Physiotherapy (Fig 19) (46)

The cases studied shows that physiotherapy plays an important role in treatment of patients suffering from frozen shoulder. Various therapeutic techniques like hot packs, ultrasound, capsular stretches, strengthening exercises and home regime have a significant effect in reducing pain, increasing range of motion and stiffness of joints in frozen shoulder.

The Usual followed Physiotherapy regime is as follows :

DAY 1-5

- Hot packs for 15 minutes so as to relax the muscles around shoulder complex.
- Ultrasonic therapy: 0.8 watts with 1 MHz frequency probe for 10 minutes for breaking the adhesions as well as relieving pain.
- Shoulder joint capsule stretching (4 times)

- Glenohumeral GH Caudal glides (4sets of 10 rep. each)
- Glenohumeral GH Posterior glides (4 sets of 10 rep. each)
- Long axis traction of glenohumeral joint (5 mins)
- Passive movements
- Finger ladder exercise
- Shoulder wheel exercise for 15 minutes
- Home regime
- Hot water fomentation
- Pendular exercises
- Wall finger climbing exercises
- Self assisted exercise.

DAY 6-10

Exercises are same while number of repetitions is increased

- Shoulder joint capsule stretching (6 times)
- GH Caudal glides (6 sets of 10 rep. each till end range)
- GH Posterior glides (6 sets of 10 rep. each till end range)
- Long axis traction of glenohumeral joint (7 times)
- Hold relax exercises (7 repts)
- Resisted exercises in available range are added (10 repts)

DAY 11-15

Exercises are kept same and the numbers of repetitions are increased.

- Hold relax exercise (10 repts)
- Resisted exercises in available range are added (15 repts)

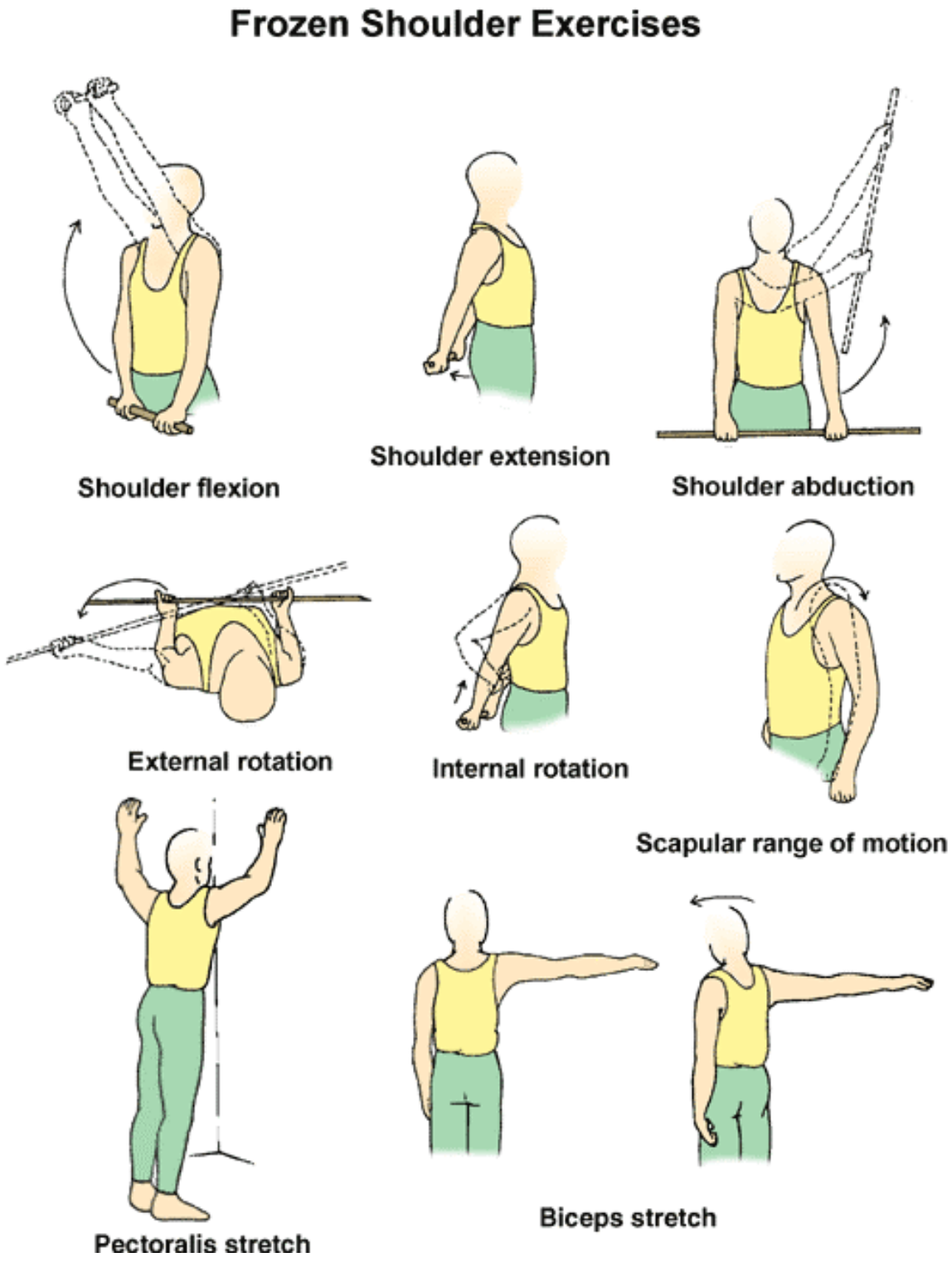

Fig 19 : Physiotherapy Exercises(46)

4. **Capsular Dilatation**

This method of treatment ought to be done under local anesthesia affected joint is injection with local analgesic to extend the capsule. This method is regularly inadequately tolerated because of pain that is experienced during the procedure of intra-articular injection. So capsular distention injections may be unfamiliar .

Surgical Treatment

The treatment of frozen shoulder should prompt the surgical treatment only after conservative management has not given any advancement. There is no positive due date to mediate medical procedure. There is no definite deadline to intervene surgery. As a general rule patients should not noticing any progress in the symptoms, after taking some form conservative management for at least 2 months. Patients those who are having significant pain and limitations can proceed with surgical intervention.

1. **Manipulation Under Anaesthesia (47)**

Manipulation under anaesthesia strategy permits to re-establishing the ROM of the shoulder in the working theatre. Quick post operative physiotherapy can be required for this strategy . Inconvenience of control is pain Disadvantage of manipulation is pain after recovering from the anaesthesia. It may be happening because of tissues stretched during the manipulation under anaesthesia. This can be potentially slow recovery process. When it adding with surgical release it induces further surgical trauma to the shoulder and may cause slow rehabilitation. (47)

2. Arthroscopic Release and Repair (Fig 20) (48)

Arthroscopy is an extra device for tending to the shoulder with frozen shoulder. Essential lesion are fixed coracohumeral tendon and rotator cuff interim with the contracted capsule including the axillary pouch on the affected joint. . These structures can be preserved by release with arthroscopic instruments. ROM of the shoulder can be maintained under arthroscopic release with manipulation, if necessary. The release can be executed either before, during, or after the manipulation (26). The manipulation may need to precede the technique to gain access to the joint. Arthroscopy allows complete evaluation of the shoulder and its anatomy as well. Any pathology that may not have been diagnosed can be addressed with this procedure. This procedure may make postoperative ROM less painful and decreases the recovery period. Operative treatment of frozen shoulder has been shown to reduce the duration of the disease and to return ROM with good prognosis. Total recovery of pain-free ROM averages 2.8 months and time taken for formal physical therapy is 2.3 months

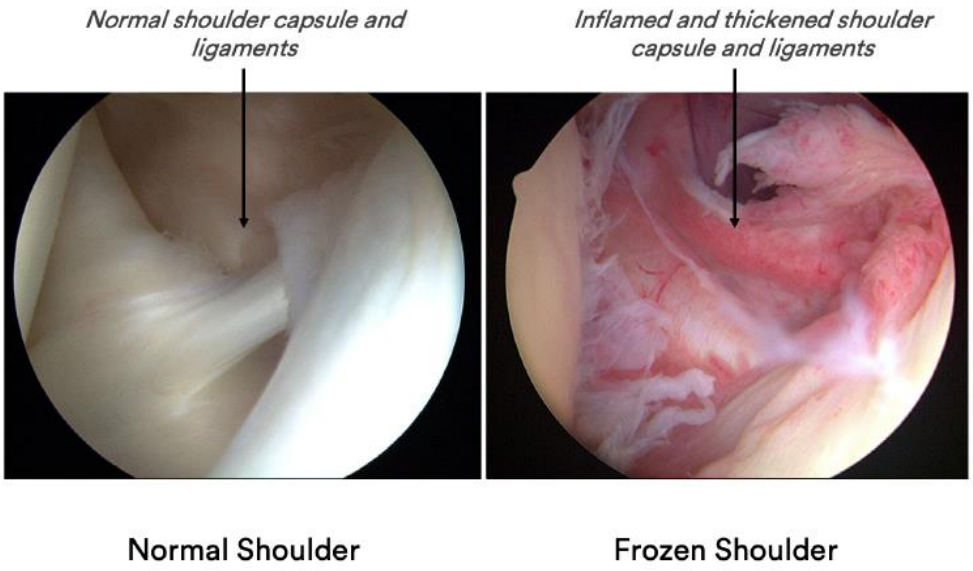

Fig 20 : Intra op arthroscopic view of frozen shoulder (48)

CALCITONIN (49)

The primary role of polypeptide hormone of calcitonin is the controlling bone calcium metabolism and calcium blood levels in the body.

It is produced by Parafollicular C - cells of the thyroid gland. It is a single chain polypeptide hormone with a 1–7 disulfide bridge at the amino terminus and a carboxy-terminal proline amide. This hormone was first discovered in 1962 and so named because of its ability to lower plasma calcium levels.

For many years calcitonin have been used to maintain and improve bone mineral density and reduce the fracture rate. However various studies showed that calcitonin could have analgesic role in different painful states.(49)

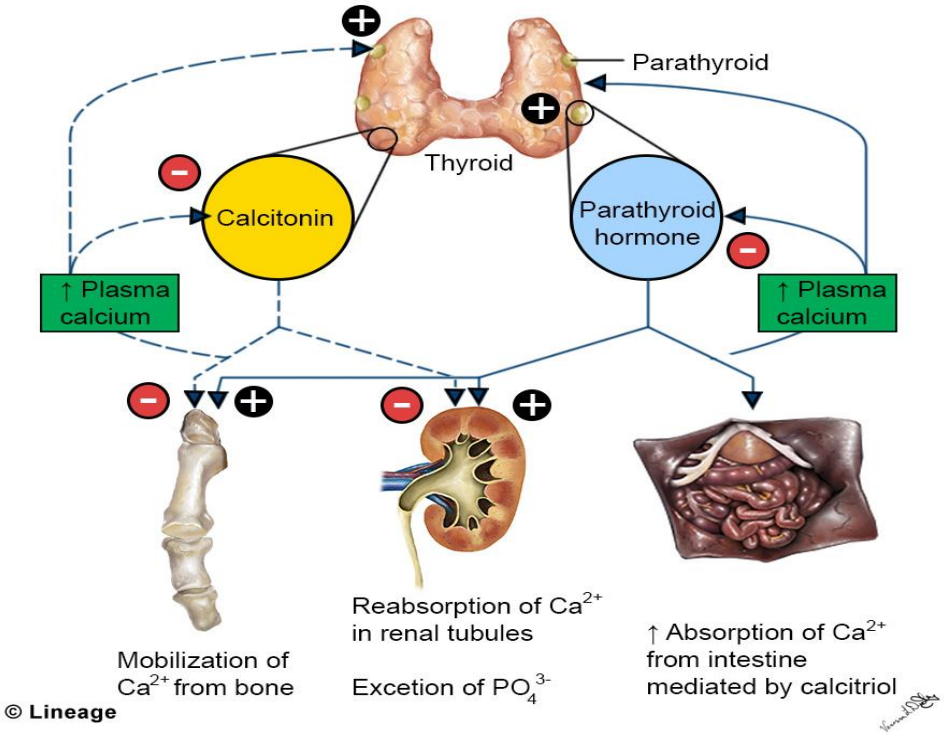

Fig 21 : Mechanism of calcitonin(49)

Many studies support the fact that calcitonin showed analgesic effect in several painful circumstances, including metastasis, painful diabetic neuropathy, migraine and reflex sympathetic dystrophy as well as neuropathic pains. After searching through online data bases, we found two reviews investigated the analgesic effect of calcitonin. Appelboom reviewed the situations including cancer metastases, osteoporotic fractures, phantom limb pain, complex regional pain syndrome and migraine. Their study suffered from lack of well-designed studies with long-term follow- ups and did not include many conditions which were discussed in our study. Mehta also came up with a well-designed, comprehensive and informative review (50). But there review just focused on the pain with origin of bone and did not study other types of painful conditions. So as the novelty of this review we are up to investigate the role of calcitonin as an analgesic agent in different painful situations by discussing the mechanism, comparing and evaluating contradictory results, including and gathering newly published data which were not reviewed before and finally drawing a clear outline for possible role of calcitonin as a feasible alternative for pain control by weighting (49)

Mechanisms

Several researches have helped reveal the mechanism of the analgesic effects of calcitonin by using different methods and animal pain models.

One theory focuses on the interaction of calcitonin with peripheral neuropathy. According to this theory, chemotherapy-mediated peripheral neuropathy may induce expression of transient receptors like melastatin-8 and ankyrin-1.

It was showed that calcitonin could inhibit the signals associated with this receptor(melastatin-8 and ankyrin-1) which contributes to analgesic function of calcitonin in peripheral neuropathy. Also, according to another theory nerve injuries can activate an unknown calcitonin- dependent signal. This signal which is

activated by calcitonin administration, results in decreased transcription of the sodium channel in dorsal root ganglion neurons. Therefore calcitonin can regulate primary afferent nerves excitability in peripheral nervous tissues by controlling the transcription of the sodium channel. The signals of calcitonin may be normally inactive due to the absence of a target, whereas nerve injuries or ovariectomy can induce these targets .According to next theory and based on serotonin role in pain processing and modulation, calcitonin has been shown to decrease serotonin transporters and increase the expression of the serotonin receptors of the thalamus.

Adhesive capsulitis

In a double-blind randomized clinical trial conducted by Rouhani et al. on 64 patients with shoulder adhesive capsulitis, the intervention group received intranasal calcitonin for 6 weeks. Considerable improvements were reported in functional scores and shoulder pain in the calcitonin group in comparison to the placebo group. Also a prospective research by Waldburger on 50 patients with the same disease in three hospitals in Switzerland showed that using calcitonin intranasaly mitigated the pain and improved shoulder function. Brue also found that subcutaneous calcitonin combined with 21 day physiotherapy showed promising effects on adhesive capsulitis

Adverse effects and safety

Salmon calcitonin is believed to be very safe, in several studies and in the post-marketing period more than 30 years and with several million patients using it every year. The main contraindication is hypersensitivity to components of calcitonin. So before systemic administration of this drug if hypersensitivity is suspected, patient can benefit from skin testing. Systemic adverse effects, including flush or nausea are more common with the parenteral or intramuscular administration than the nasal spray form.

In clinical trials, frequency of adverse event were generally comparable between calcitonin and control group. For calcitonin, the patients frequently reported transient local involvements likes tingling of the nasal route, rhinitis, sneezing and nasal mucosal irritation. Of these adverse effects, 97% were considered mild to moderate, and up to 10% of patients receiving calcitonin experience these side effects. Over- all, calcitonin compares favorably versus other analgesic drugs in terms of adverse effects, precautions, interactions with other treatments and contraindications. Because of the transient not permanent suppression of osteoclasts and according to longstanding clinical trials, it seems that there are to no potential for detrimental effects on skeletal system and other organs during long-term medication.

Several reasons can be proposed for why calcitonin should be used when usual analgesics fail control pain. Firstly, according to the review by the authors, patients can experience near-complete relief of symptoms in many painful circumstances, especially in acute pain and neuropathies. Secondly, the drug is safe, simple to administer and does not cause significant adverse effects on different metabolism pathways. Thirdly, calcitonin can be useful medications for whom with renal, liver and intestinal problems to reduce the required dose of analgesics. However in healthy patients this advantage is less prominent due to economical factor, possibility of reduced patient compliance due to a longer list of prescribed drugs and finally meager benefits for healthy patients.

Various articles regarding Adhesive Capsulitis - pathogenesis and treatment modalities

In 1998 study done by bunker suggested that adhesive capsulitis is a commonly recognized but poorly understood cause of painful and stiff shoulder. Frozen shoulder syndrome was first described by Duplay in 1872 (Duplay ES 1872). In 1934, Codman used the term Frozen shoulder to describe this condition . Reidel was the first to suggest that the basic pathology of shoulder stiffness may be localised to the joint capsule . Early investigators suggested adhesive capsulitis as either an inflammatory process or a fibromatosis(51)

A study in 2017 concluded that The exact etiology of frozen shoulder remains debated and numerous risk factors for this pathology have been proposed. The role of some hormonal and metabolic diseases, such as diabetes, hyper-, and hypothyroidism, has been demonstrated to be relevant role in the development of frozen shoulder. Numerous other potentially relevant factors have been described, which require further research to be. confirmed. Recent evidences from molecular biology suggest that an underlying a specific pro- inflammatory condition could represent a predisposing risk factor for the development of frozen shoulder(52)

A study done in 2019 , synovial capsular fibroblast were obtained from frozen shoulder patients and evaluated for fibrosis related molecule expression and cell substrate adhesion by Synovial capsular fibroblasts. Following tests were done cell-culture,Quantitative-PCR,IHC,Cell adhesion substrate assay.The study determined apoptotic effect of salmon calcitonin treatment on fibroblast(53)

A study done in 2020 , Glenohumeral capsular biopsies were reported in 30 studies. Fifteen studies investigated were classified as association studies. Three studies investigated the pathophysiology in an animal studies. A state of low grade inflammation, as is associated with diabetes, cardiovascular disease and thyroid disorders, predisposes for the development of frozen shoulder. An early immune response with elevated levels of alarmins and binding to the receptor of advance glycation end products is present at the start of the cascade. Inflammatory cytokines, of which transforming growth factor-β1 has a prominent role,

together with mechanical stress stimulates Fibroblast proliferation and differentiation into myofibroblasts. This leads to an imbalance of extracellular matrix turnover resulting in a stiff and thickened glenohumeral capsule with abundance of type III collagen. (54)

A study in 2018 concluded that Studies characterizing the pathophysiology of FS are inconclusive but suggest both inflammation and fibrosis of the joint capsule mediated by cytokines, growth factors , matrix metallo proteins (MMPs) , and immune cells. Variations in diagnostic criteria, timing-of sampling, and techniques used for these analyses might affect the reported results and conclusions. To enhance our understanding for disease continuum, better characterizing the biology of these processes at clearly defined stages will be needed. Further basic studies that use standardized protocols are imperative to identify the role of cytokines, growth factors, MMPs, and immune cells (55)

In 2016 a study done concluded that The most typical features of AC are pain associated with progressive stiffness and loss of external rotation movements of the shoulder ,The loss of other motion may also be present, depending on the area of the capsule most affected. Pain may be reported anteriorly or posteriorly, occasionally extending over the biceps tendon, especially while resting in bed; however, in most cases, pain cannot be localized reliably.The diagnosis of AC is based mainly on clinical findings. Plain film generally plays no role in diagnosing this condition. Ultrasound can be used primarily to detect thickening of the coracohumeral ligament and synovial hypertrophy at the rotator cuff interval. MR and MRA have demonstrated high diagnostic accuracy in detecting a number of features suggestive of adhesive capsulitis, including inferior glenohumeral ligament hyperintensity, capsular and coracohumeral ligament thickening, poor capsular distension, and synovial hypertrophy and tissue scarring at the rotator interval (56)

In 2019 a study by Lauren and Elizabeth regarding the treatment option concluded that Based on the natural history of the disease, early corticosteroid injection has a role in shortening the overall duration of symptoms. Patients should be counseled that NSAIDs and corticosteroid injections do not cure the problem;For patients with diabetes who may have undue metabolic disarray from corticosteroid injection,

ECSWT may have a role in symptom relief. Most patients will see complete resolution of symptoms with non- surgical management. When surgical intervention is required, the ideal technique should include both anterior and posterior capsular release as well as rotator interval release specifically including release of the CHL. When combined with a gentle MUA, circumferential capsular release is possible without risking injury to the axillary nerve. An inter scalene block can be used to provide enhanced pain relief . To avoid complications, aggressive MUA should be avoided, care must be taken with inferior release, and all patients should have portable AP, lateral, and axillary imaging (57)

A study in 2010 on physiotherapy intervention concluded that adhesive capsulitis is a challenging condition for both the physical therapist and patient. It is important for clinicians to make an accurate diagnosis and assessment in order to best choose their interventions. By understanding the published evidence related to the rehabilitation of patients with adhesive capsulitis, both therapists and patients will benefit from an integrated, multi-faceted, evidence-based approach to intervention (58)

In 2020 a double blinded RCT was done. All three groups were homogenous and comparable regarding their age, sex ratio, pre treatment pain score, disability score and range of motion. There was significant improvement ($p < 0.05$) post treatment in all three groups with respect to pain score, disability score and range of motion. Supra-scapular nerve block (SSNB) with non invasive rehabilitation group patients demonstrated better improvement in all parameters examined, which was statistically significant in pain score, disability score and internal rotation but was statistically equivalent for total range of motion and external rotation as compared to shoulder injection group.SSNB in combination with non invasive rehabilitation is an effective and safe mode of treatment for idiopathic frozen shoulder. Present study also proves that SSNB with NIR is a more effective mode of treatment for idiopathic frozen shoulder as compared to NIR alone or in combination with Intra articular injection. three groups were homogenous and

comparable regarding their age, sex ratio, pretreatment pain score, disability score and range of motion (59)

A meta analysis of RCT was done in 2019 done concluded that ,this is the first meta-analysis from recent published RCTs to compare the efficacy and safety of intra-articular injection and subacromial injection for patients with Frozen Shoulder. The most important finding of the present meta-analysis was that intraarticular injection was associated with a significant reduction in VAS score, with a benefit lasting for at least 3 month. There was no significant difference between groups regarding the risk of adverse effects. Among various treatment approach, subacromial injection and intra- articular injection were commonly used, however, the intra-articular injection was technically more demanding without radiologic guidance compared to subacromial injection which was more easily to accomplish. It was considered to be relatively safe and cost-effective with a rapid and satisfactory outcome. The optimal approach of corticosteroid injection remained controversial. It was well known that intra-articular corticosteroid was associated with short term effect on pain relief in FS. Previous articles have shown that subacromial injection was as effective as intra-articular injection in reducing pain Rizk et al. re- ported that intraarticular and subacromial injections achieved similar pain scores at 4 weeks, 12 weeks, and 24 weeks. However, Kim et al. indicated that the efficacy of corticosteroid injection into the subacromial space in FS was inferior to intra-articular injection up to 12 weeks. In our study, 5 RCTs with 307 patients showed the outcome of VAS (0–10cm) from different follow up period. The present meta- analysis indicated that intra-articular injection showed superior out- come for reducing pain in FS at 1 month, 2 month and 3 month.Intra-articular injection of racorticosteroid was associated with an improved outcomes for pain relief compared to subacromial injection (60)

In 2016 a RCT study compared Intra-articular injection of triamcinolone with NSAID (naproxen) in diabetic frozen shoulder patients. This study was done only in diabetic patients, and adhesive capsulitis due to any other underlying causes were excluded from the study. Range of motion was detected precisely by goniometer. Also to guarantee the maximum effect of treatment, injections were done under sonography

guide and also patient in NSAID group were requested to give the remnant drugs back to researcher. Patients were followed for 6 months and evaluated within 5 visits.After 6 months of follow-up, we did not find any significant different between 2 groups according to flexion, abduction, external rotation, internal rotation and also pain score. Range of motion in patients of both groups almost returned to normal range (61)

IN 2015 Review article stated that,Pharmacological treatment for adhesive capsulitis em-ploys the use of oral drugs such as nonsteroidal anti-in-flammatory drugs (NSAIDs) and corticosteroids. NSAIDs,are used across all stages of treatment to alleviate pain.Yet some studies have questioned the effectiveness of NSAIDs in pain control.The initial conservative approach of drug therapy and stretching usually follows diagnosis.We believe that at the early stage of frozen shoulder aninflammatory cytokine-targeted treatment may be used, whereas at the stage when the condition is more progressed a treatment that decreases scar,deposition,accelerates capsular remodeling may be effective. . If symptoms prolong for too long and a conservative management of longer than three months becomes too burdensome for the patient, then surgical-intervention should be considered (62)

In 2015 A study concluded that Frozen shoulder is a common disease which causes significant morbidity. Despite over a hundred years of treating this condition the definition, diagnosis, pathology and most efficacious treatments are still largely unclear. This review of the recent evidence base highlights key areas for future research in particular with regard to the increasing role of arthroscopic capsular release as a treatment. High quality adequately powered randomized controlled trials comparing the most common interventions to a sham procedure would be the ideal way to improve the current evidence base. However these are difficult studies to construct and recruit for. Frozen shoulder can be such an intensely painful condition that in severe cases one could consider that an option of no treatment as part of a control group could be considered to be unethical. Given these real world problems in construction of clinical trials the optimum area to concentrate further research is in comparing other non surgical treatment options with other surgical treatment (63)

In 2014 a study concluded that Regardless of what form of non-operation intervention used and despite the benign natural history of the disease, some patients fail to achieve desired outcomes withnon-operative management. Surgical treatments may provide long term improvement but may carry surgery related risks. The management of frozen shoulder amongst shoulder surgeons varies, both with regards to non-surgical and surgical options. A substantial proportion of surgeons base their choice of treatment on personal experience and training rather than published evidence. Our results support the need for high quality clinical trials to compare the treatment options available to the shoulder surgeon (64)

In 2015 study on Follow-up of 36 Idiopathic Frozen Shoulder Patients concluded, Shoulder Accelerated Rehablitation protocol is a non-invasive, easy to follow and reproduce home based exercise program effective in early improvement of pain and disability in patients with frozen shoulder. It helps the patient to get back to the pre-disease status as early as possible. , patients who followed the home exercise programme properly were early to recover and had good results even at the end of 2 years of follow up. All the patients improve with physical therapy (SHARP) alone. Home based heat therapy was advised as per the patient tolerance to pain especially after a session of exercises (65)

In 2009 A Study on oral steroids vs Intra-Articular steroid concluded that On trial of 28 participants found a better cure rate (defined as able to achieve 90% of normal range of glenohumeral motion for abduction and external rotation) in the steroid injection group compared to oral steroids after one week (RR = 0.22 (95% CI 0.06 to 0.84)) but this was not statistically significant at weeks 2 or 3 (RR=0.65 (95% CI 0.42 to 1.01) and RR=0.80 (95% CI 0.62 to 1.03) respectively). A significant difference in pain between the two groups was also reported after one week although which group had better scores was not reported, and there were no differences between groups at weeks 2 or 3 (66)

In 2017 study concluded that The present survey, involving a representative sample of pharmacy users in taking NSAIDs, suggested that most of the individuals were not aware of side effects of NSAIDs, or their interactions with other classes of drugs. However, study subjects could correctly mention a considerable

number of specific drugs pertaining to this class. How- ever, more than half of participants declared that they took NSAIDs based on their opinion and only in about 30% of cases a physician and/or a pharmacist was involved, implying that the role of medical professionals in prescribing NSAIDs and their use in community is rather limited. The most commonly used NSAIDs were those containing the following active ingredients acetaminophen, ketoprofen and ibuprofen.

In conclusion, there is limited knowledge about NSAIDs side effects and their interaction with other drugs among the general population. There is an urgent need to educate the general public about NSAIDs in general, their appropriate use and the respective adverse effects (67)

In 2016 a study ,double blinded RCT was conducted on 64 patients suffering from shoulder adhesive-capsulitis.The intervention and control group were given intranasal calcitonin and placebo for 6 weeks respectively.For both the groups physiotherapy and NSAIDS were administered correspondingly.The patient were evaluated for pre and post treatment for shoulder pain and Range of motion.Shoulder functional outcome was evaluated using Disability of arm ,shoulder and hand and Disability Index and Health assessment questionnaire disability criteria.The study concluded that in post treatment followup , shoulder pain ROM, and functional scores were significantly improved in both group.However the improvement in calcitonin group was more effective in than that of of placebo group.(68)

A-study done in 2018 regarding association between parkinson and frozen shoulder concluded that, Due to a severe impairment of posture, patients affected by PD show an increased thoracic kyphosis (camptocormia) and decreased mobility of the trunk that can yield a humeroacromial impingement syndrome and capsulitis, resulting in inflammation of the bursa, shoulder pain and reduction of movement. Furthermore, kinematic of the shoulder is allowed by the combined movement of the humerus, the scapula, the clavicle, the thoracic wall and thoracic spine. The thoracic spine and wall mobility are severely impaired in the parkinsonian patient, thus limiting the shoulder motion. The postural alteration observed in PD is the primum movens for shoulder pathology, since anterior tilt of the scapula, which occurs with the increment of thoracic kyphosis,

yields to a subacromial impingement. A closed loop is then created, as the rigidity of the shoulder causes further alteration in the posture, which worsens the impingement(69)

A RCT in 2015 concluded that treatment group after one CCH injection, no improvements in individual parameters met the criterion of the minimally clinically important difference Therefore, one CCH injection did not provide clinically important improvements in ROM, function, or pain scores. As an example of a primary efficacy variable, at 30 days for active forward elevation (flexion) the means in degrees for placebo, 0.145 mg CCH, 0.29 mg CCH, and 0.58 mg CCH were 125°, 132°, 130°, and 140° (p \ 0.01 for 0.58 mg versus placebo), respectively. Regarding adverse events, 100% of patients who received CCH injections experienced injection-site tenderness, which resolved in a mean of 5 ± 4 days, and biceps ecchymosis, which resolved in a mean of 9 ± 5 days. Six of 60 patients (10%) had mild injection-area edema, which resolved in a mean of 1 ± 0.7 days. Forty-six of the 60 patients (76%) entered the open-label phase as they did not reach treatment thresholds with either one placebo or CCH (various doses) injection. Forty-five (98%) of these patients reached treatment thresholds with one or CCH injections, 5 to 6 weeks apart. The majority (n = 24) responded to one or two additional injections (n = 20). Adverse events were as described above. There were no adverse events or recurrence of adhesive capsulitis at 1 to 5 years of long-term follow up among the patients who were accounted for We suggest that CCH injection(s) may have merit for patients with adhesive capsulitis in restoring shoulder ROM, increasing function, and reducing pain. Additional FDA-regulated clinical trials are planned which will compare collagenase injection(s) with a placebo in larger numbers of patients in randomized and blinded studies. In Study 2 we confirmed that, using ultrasound guidance in the injection method, the injections to the anterior shoulder capsule were extraarticular. This is extremely important because the type II cartilage of the glenohumeral, joint and other normal collagen-containing structures are potentially at risk for degradation by collagenase (70)

MATERIALS AND METHODS

Source of Data

Data was collected from patients who reported to the Orthopedic department OPD in KLE'S Dr. Prabhakar Kore Hospital & Medical Research Centre and Charitable Hospital in Belagavi over a period of one year from1st January 2021 to 30th December 2021.

Study Design: PROSPECTIVE DOUBLE BLINDED RANDOMIZED CONTROLLED TRIAL

Duration of data collection: 1 YEAR

Study Period: January 2021 - December 2021

Study Population : Patients who came to the outpatient orthopedic department and were diagnosed with shoulder adhesive capsulitis

Randomization and Study design :

Patients were divided into 2 groups, the intervention group and control group by computer randomization using Microsoft Randomizer version 2017.

Both the patient and the primary investigator were be blinded. The intervention group will receive intranasal calcitonin 200 units/day for 6 weeks along with Home based physiotherapy and NSAIDs. The control group will be receiving only homebased physiotherapy and NSAIDS.

Method:

Following the approval of ethics committee and the consent, the double blinded RCT will be conducted on patients with shoulder adhesive capsulitis. Those skeletally mature patients with shoulder pain and limitation in ROM who were clinically diagnosed with clinical symptoms along with the diagnostic criteria of the disease.

The eligible patients who signed the inform consent forms were assigned into 2 parallel groups

Intervention group (group A) and Control group (group B), by Microsoft Randomizer.

Intervention group-is given 200 units of intranasal calcitonin per day for 6 weeks while control group was given Physiotherapy and NSAIDS. Medication will be administered by a non-biased observer and will be evaluated by the primary investigator. During the 6-week treatment period, the patients were excluded from the study if they were not intended to continue the treatment or if they suffered from intolerable pain or side effects.

Patients were blinded to receive calcitonin by the observer who was responsible for randomization and drug administration.

The rest of the observer were also blinded to which spray had been administered till end of the study.

For both groups physiotherapy and NSAIDS were administered correspondingly.

Home Physiotherapy for 6 weeks were given, which includes Hot moist pack (15 to 20 mins)/2 times daily, Posterior Capsule Stretching 3 sets of 10 holds daily, Wall ladder exercises, Caudmans pendular exercises in flexion, extension, abduction and circumduction 3 sets of 10 reps each, Scapular retraction and elevation 1 set 3 times a day.

NSAIDs are given till pain relief and discontinued if pain is relieved

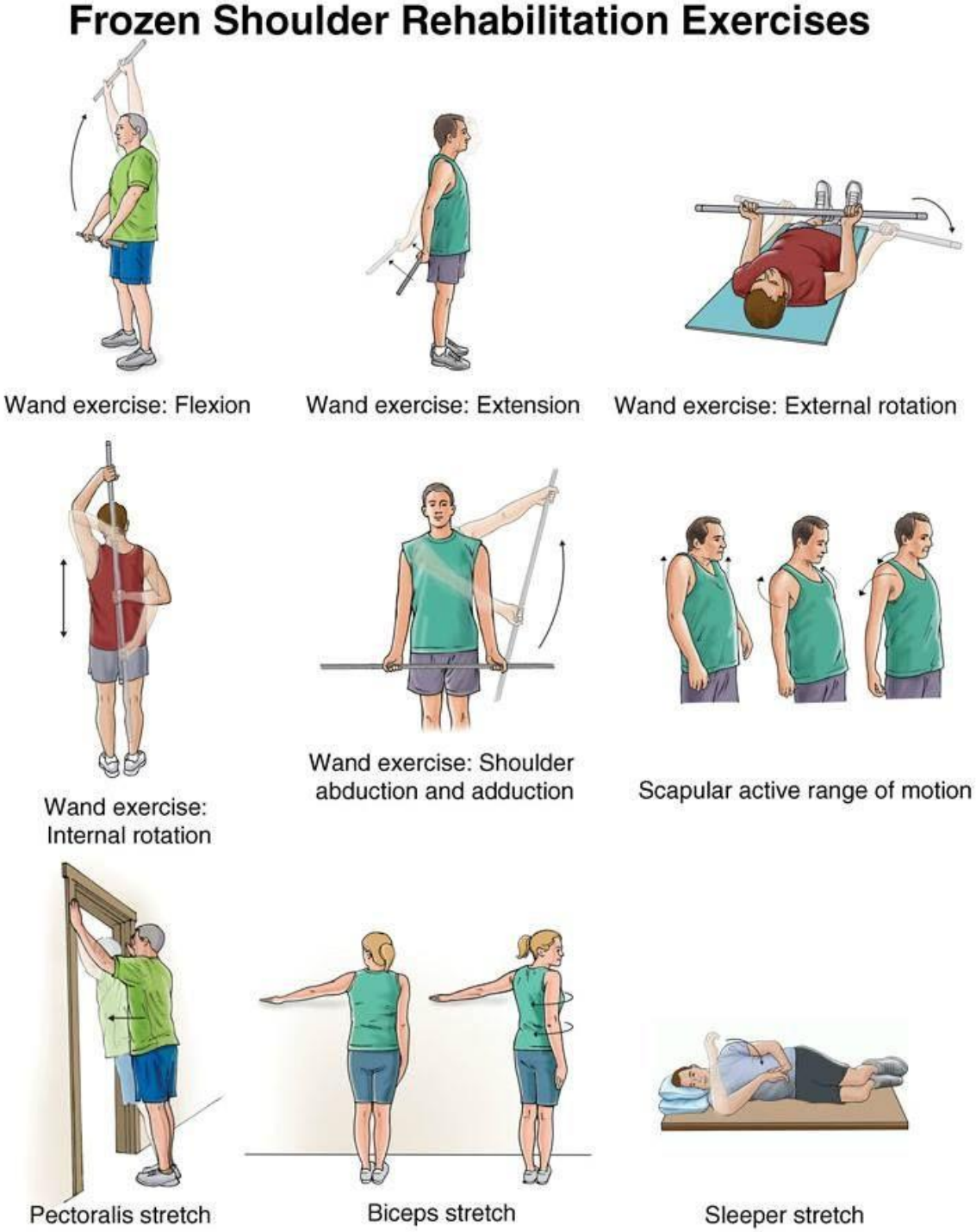

Fig 22: Rehabilitation exercises (71)

Pre requisites:

- X-ray shoulder Anterior-Posterior view
- Blood-test

  CBC, ESR, S.Calcium, S.Creatinine, RBS, SGPT, Total Cholesterol

PRIMARY OUTCOME VARIABLES

• Range of motion (ROM) assesed passive pain free motion with
goniometer (expressed in percentage of normal shoulder per contralateral shoulder).

Goniometer (Fig 22) is a device that measures an angle or permits the rotation of an object to a definite position. In orthopedics, the former description applies more. The art and science of measuring the joint ranges in each plane of the joint are called goniometry.

A goniometer can evaluate both active as well as passive range of motion.(72)

Positioning plays a vital part in goniometry because it helps to place the joints in a zero starting position or a neutral position and helps to stabilize the proximal joint segment. The examiner stabilizes the proximal joint component and then carefully moves the distal component of the joint through its entire available range of motion until reaching the end feel.

- After estimating the available range of motion and the examiner returns the distal component to the starting position. The examiner palpates the relevant bony landmarks and aligns the goniometer.
- The examiner records the starting measurement and removes the goniometer, and the patient moves the joint through the available range of motion.
- Once the joint has run through the available range of motion, the examiner replaces and realigns the goniometer and reads and records the measurement.

- The examiner repeats the measurement three times and calculates the average; this is the active range of motion measurement.
- The examiner compares the reading with the contralateral side.
- The joint is then moved passively through its passive range of motion (PROM), and the steps mentioned above are repeated to measure PROM accurately.
- Care is necessary to make sure the patient does not move his body while moving the joint, thereby ensuring accurate measurement.

Positioning significantly influences the tension in soft tissue structures like capsules, muscles, and ligaments, which envelope a joint. Any position which tenses the soft tissue structures will lead to a limited range of motion compared to a position where the structures are lax.

It is vital to make sure that the same testing position during successive measurements to ensure that the amounts of tension remain constant in the soft tissue as compared to past measurements. This approach assures the obtaining of similar results. Any change in position will lead to erroneous readings.

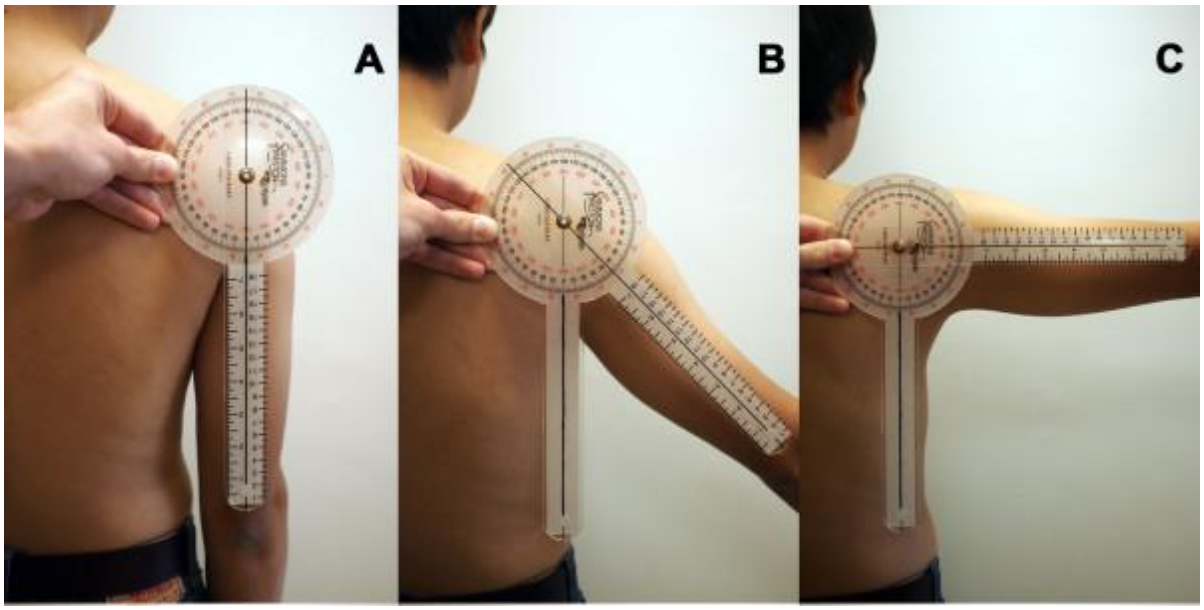

Fig 23 : Goniometer for range of motion (72)

SECONDARY OUTCOME VARIABLES

Functional outcome evaluation by

• The Shoulder Pain and Disability Index (SPADI) assessed at pre treatment and at 6 weeks (73)

The Shoulder Pain and Disability Index (SPADI) (Fig 23) is a self-administered questionnaire that consists of two dimensions, one for pain and the other for functional activities. The pain dimension consists of five questions regarding the severity of an individual's pain. Functional activities are assessed with eight questions designed to measure the degree of difficulty an individual has with various activities of daily living that require upper-extremity use. The SPADI takes 5 to 10 minutes for a patient to complete and is the only reliable and valid region-specific measure for the shoulder. (73)

Scoring instructions To answer the questions, patients place a mark on a 10cm visual analogue scale for each question. Verbal anchors for the pain dimension are ‘no pain at all’ and ‘worst pain imaginable’, and those for the functional activities are ‘no difficulty’ and ‘so difficult it required help’. The scores from both dimensions are averaged to derive a total score

Interpretation of scores Total pain score: x / 50 x 100 = %

Note: If a person does not answer all questions divide by the total possible score, eg. if 1 question missed divide by 40)

Total disability score: x / 80 x 100 = % (Note: If a person does not answer all questions divide by the total possible score, eg. if 1 question missed divide by 70)

Total SPADI score: x / 130 x 100 = % (Note: If a person does not answer all questions divide by the total possible score, eg. if 1 question missed divide by 120)

The means of the two subscales are averaged to produce a total score ranging from 0 (best) to 100 (worst).
Minimum Detectable Change (90% confidence) = 13 points

SPADI (SHOULDER)

Name _____ Date_____

PAIN SCALE	
How severe is your pain:	
1. At its worst.	No pain 0 1 2 3 4 5 6 7 8 9 10 Worst Pain Imaginable
2. When lying on involved side.	No pain 0 1 2 3 4 5 6 7 8 9 10 Worst Pain Imaginable
3. Reaching for something on a high shelf.	No pain 0 1 2 3 4 5 6 7 8 9 10 Worst Pain Imaginable
4. Touching the back of your neck.	No pain 0 1 2 3 4 5 6 7 8 9 10 Worst Pain Imaginable
5. Pushing with the involved arm.	No pain 0 1 2 3 4 5 6 7 8 9 10 Worst Pain Imaginable
DISABILITY SCALE	
How much difficulty did you have:	
1. Washing your hair.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
2. Washing your back.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
3. Putting on an undershirt or pullover sweater.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
4. Putting on a shirt that buttons down the front.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
5. Putting on your pants.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
6. Placing an object on a high shelf.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
7. Carrying a heavy object of 10 pounds.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help
8. Removing something from your back pocket.	No difficulty 0 1 2 3 4 5 6 7 8 9 10 So difficult required help

Fig 24 : SPADI scoring system (73)

DEMOGRAPHY AND HISTORY

- Age
- Gender
- Occupation
- Weight
- height
- Dominant side
- Involved site
- H/o shoulder trauma
- H/o of prior shoulder surgery
- H/o shoulder pain related treatment
- Duration of frozen shoulder
- Nocturnal pain
- H/o systemic diseases
- ROM in flexion, extension and external rotation

Inclusion Criteria:

- Above 18 years both sex
- Cases of adhesive capsulitis i.e. shoulder pain with reduced range of motion

Exclusion Criteria:

- Previous shoulder surgery
- Patients with h/o intra articular steroid
- Symptomatic contralateral shoulder
- Accompanying metabolic disorders and parathyroid disorders
- Refusal of consent.
- Secondary cases of Adhesive Capsulitis
- Patients with evidence of Gleno humeral arthritis and complete Rotator cuff tear

Sample size calculation

Based on previous study by Alireza rouhani Et.Al. Post treatment Nocturnal pain in cases was 43% and in control was 69% and minimum expected difference between two groups will be 35.

The sample Size calculation is done using the following formula :

$$n=\frac{(Z\alpha+Z(1-\beta))2(P1(100-P1)+P2(100-P2))}{(d)2}$$

Where

Zα= Standard table value for 95% CI = 1.96

Z(1-β) = Standard table value for 80% Power = 0.84

P1= proportion in group 1= 49%

P2= Proportion in group = 69%

d=precision or expected difference=35

$$n=\frac{(1.96+0.84)2((49(100-49)+69(100-69))}{(35)2}$$

n=29 each group

Proposed method of Statistical data analysis:

For different parameters contingency tables are prepared with respect to the three groups. To check the association between the groups and the categories of the parameters, Chi-Square test is applied. A value of $p<0.05$ is considered as significant.

To ascertain the association between some specific parameters cross tables are constructed. For these tables Chi-square test is applied.

RESULTS

This study was conducted in KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi , from January 2021 to December 2021.

In total, 58 patients diagnosed with adhesive capsulitis were randomized into interventional (patients receiving calcitonin nasal spray, NSAIDs and physiotherapy) and control (patients receiving only NSAIDs and physiotherapy) groups. These groups were studied for the effect of Intranasal calcitonin along with NSAIDs and physiotherapy versus NSAIDs and physiotherapy alone on the pain relief and functional outcomes of patients with adhesive capsulitis.

Data collected was included into spreadsheets of Microsoft excel. The data was analysed and the results obtained were tabulated as represented below.

'P' value less than 0.05 considered significant statistically

Results: A total of 58 subjects were present in the final analysis.

1. **Population distribution in study (Table 2)**

Descriptive analysis of group in the study population (N=58)

INTERVENTION GROUP - Patients receiving Calcitonin intra nasal spray along with NSAIDs and physiotherapy.

CONTROL GROUP - patients receiving only NSAIDs and physiotherapy.

Group	Frequency	Percentages
CONTROL	**29**	**50%**
INTERVENTIONAL	29	50%
TOTAL	58	100%

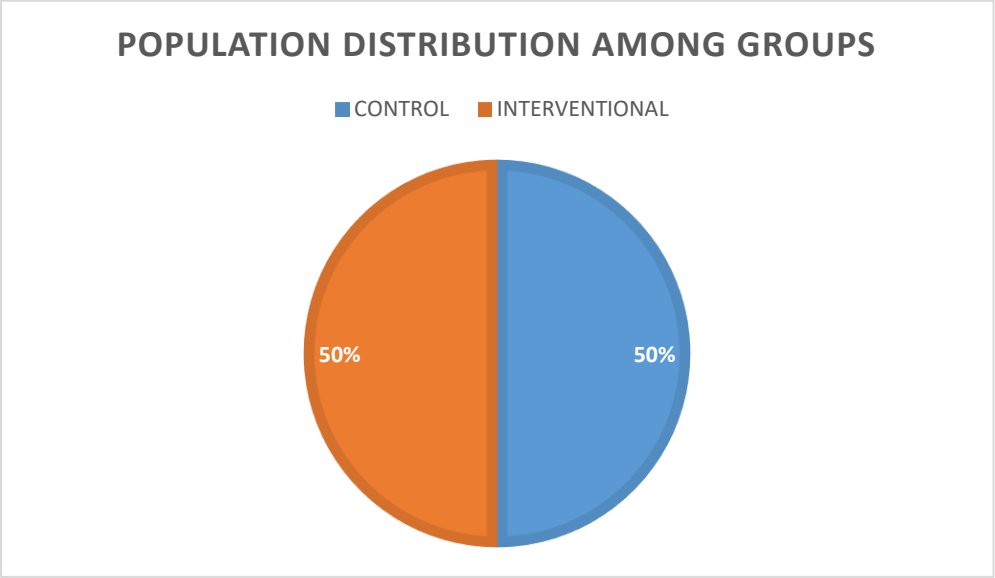

Fig 25 : Population distribution in the study groups

Among the study Population 29(50%) participants were in intervention group and remaining 29(50%) participants were in control group.

2. Gender distribution in the study (Table 3)

	CONTROL GROUP		INTERVENTION GROUP	
GENDER	**NUMBER**	**%**	**NUMBER**	**%**
FEMALE	18	62.07	18	62.07
MALE	11	37.93	11	37.93
TOTAL	29	100.00	29	100.00

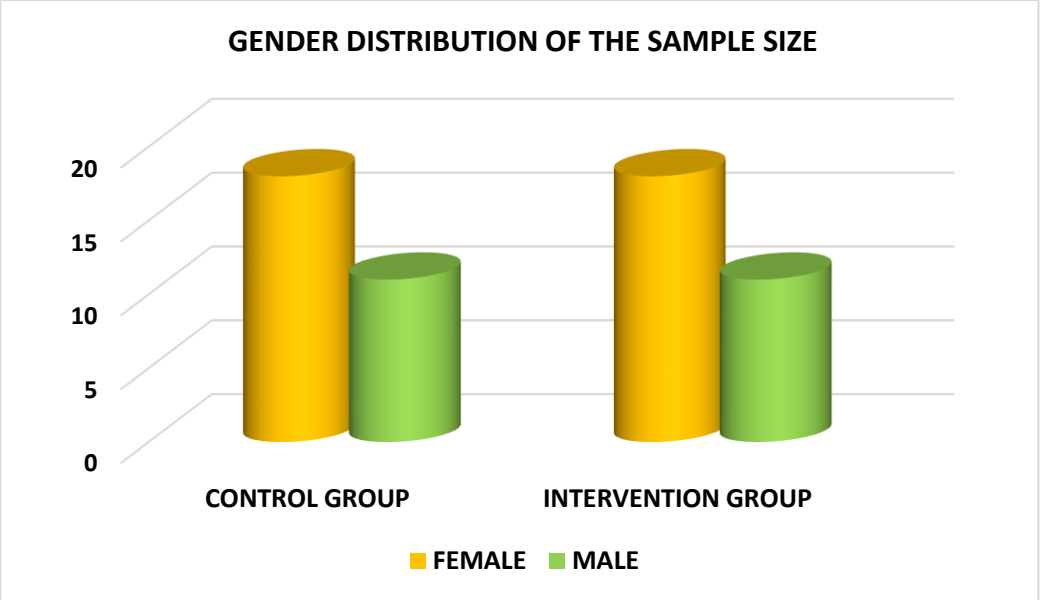

Fig 26 : Gender distribution amongst both groups

In both the groups out of 29 patients, 18 were female and 11 were male.

3. Age distribution in the study (Table 4)

	CONTROL GROUP		INTERVENTION GROUP	
AGE	**NUMBER**	**%**	**NUMBER**	**%**
40 - 49	2	6.90	7	24.14
50 - 59	14	48.28	15	51.72
60 - 69	13	44.83	7	24.14
TOTAL	29	100.00	29	100.00

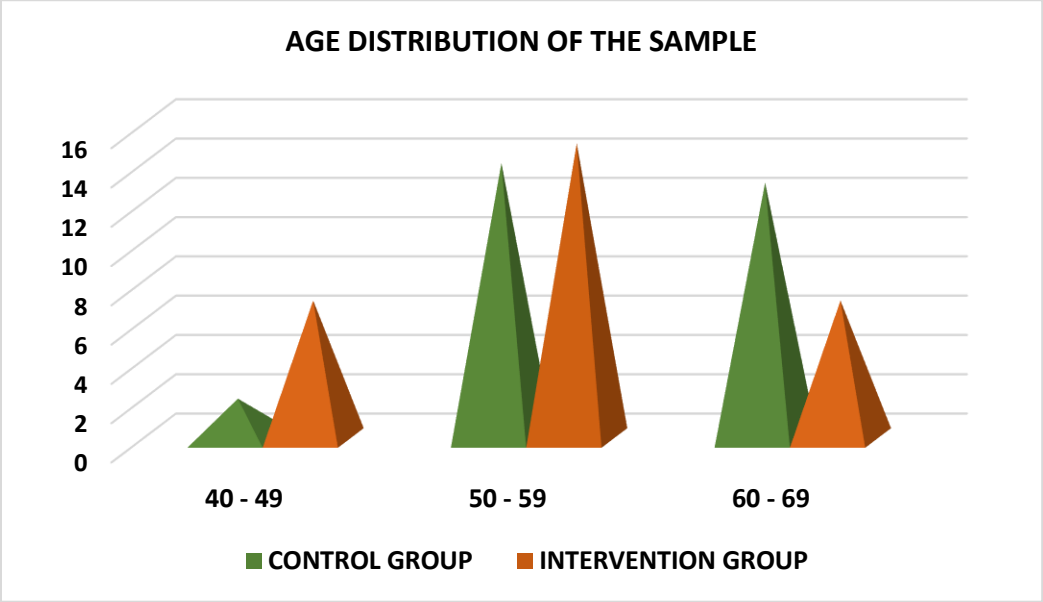

Fig 27 : Age distribution of sample size

In both groups, the maximum number of participants belonged to the 50-59 (55+-5) yrs age group.

To compare the control and intervention group age parameters, p values are calculated using student's unpaired t test (Table 5)

	CONTROL GROUP				INTERVENTION GROUP					
	MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
AGE	57.83	5.33	49	69	55.14	6.00	44	67	0.0763	NS

There was no significant difference between the age parameters of both groups.

4. **The following tables compare Pre-treatment patients' clinical specifications from both groups**

In the following contingency tables (where numbers are given) p values are calculated using chi-square test

(i) **The following table compares the duration of symptoms between both groups**: (Table 6)

DURATION OF SYMPTOMS									
CONTROL GROUP				INTERVENTION GROUP					
MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
4.10	1.92	1	8	4.00	1.73	1	7	0.8300	NS

The mean duration of symptoms for the control group was 4.10 months and for the intervention group was 4.0 months. This was not significant.

(ii) **The following table compares pre treatment nocturnal pain b between both groups**: (Table 7)

	NOCTURNAL PAIN					
	CONTROL GROUP		INTERVENTION GROUP			
	NUMBER	**%**	**NUMBER**	**%**	**p VALUE**	**INFERENCE**
	21	72.41	18	62.07		
	8	27.59	11	37.93	0.4013	NS
TOTAL	29	100.00	29	100.00		

THE NOCTURNAL PAIN IS MORE OR LESS THE SAME IN THE TWO GROUPS

(iii) The following table compares history of systemic diseases between the study population of both groups (Table 8)

	CONTROL GROUP		INTERVENTION GROUP			
SYSTEMIC DISEASE	**NUMBER**	**%**	**NUMBER**	**%**	**p VALUE**	**INFERENCE**
DM	11	37.93	11	37.93	0.9846	NS
HTN	1	3.45	2	6.90		
HTN DM	3	10.34	3	10.34		
HYPOTHYROIDISM	1	3.45	1	3.45		
NIL	13	44.83	12	41.38		
TOTAL	29	100.00	29	100.00		

In the control group, 11 participants had Diabetes Mellitus, 1 was hypertensive, 3 had diabetes mellitus and hypertension, 1 had hypothyroidism and 13 had no systemic diseases.

In the intervention group, 11 participants had Diabetes Mellitus, 2 had hypertension, 3 had diabetes mellitus and hypertension, 1 had hypothyroidism and 12 had no systemic diseases.

This difference between the data was not statistically significant, hence proving that these risk factors do not have a direct association with development of adhesive capsulitis.

(iv) The following table compares pre treatment Random Blood Sugar (RBS) and Serum Calcium levels between both groups : (Table 9)

	CONTROL GROUP				INTERVENTION GROUP					
	MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
S. CALCIUM	9.09	0.55	7.7	10.1	8.84	0.59	7.6	9.7	0.0992	NS
RBS	140.10	34.26	85	221	140.03	39.31	85	224	0.9943	NS

From the table above, we can see that the comparative data was statistically not significant.

5. **Pre-treatment shoulder pain and functional outcome in both groups (Table 10)**

	CONTROL GROUP				INTERVENTION GROUP					
	MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
FLEXION	111.55	18.18	75	140	107.41	19.67	75	145	0.4090	NS
EXT ROTATION	42.07	11.77	20	65	37.59	13.40	5	60	0.1813	NS
ABDUCTION	96.03	17.18	70	140	98.45	21.13	30	140	0.6351	NS
SPADI	84.26	5.31	74.3	94.3	82.20	5.07	71.5	93.2	0.1369	NS

Shoulder ROM was expressed by percentages (%) shoulder in comparison with the contra-lateral (non-involved).

SPADI: Shoulder Pain and Disability Index

Patients were evaluated with regard to shoulder range of motion and SPADI pre-treatment, and it was revealed that there were no significant differences between the two groups.

6. Post-treatment shoulder pain and functional outcome in both groups (Table 11)

POST TREATMENT

(AT 6 WEEKS)

	CONTROL GROUP				INTERVENTION GROUP					
	MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
FLEXION	122.76	15.96	75	145	135.69	15.45	105	165	0.0027	VS
EXT ROTATION	49.31	10.41	25	65	52.69	11.18	25	70	0.2387	NS
ABDUCTION	105.86	16.15	75	150	126.55	21.68	60	160	0.0001	HS
SPADI	66.04	3.38	59.8	71.9	57.23	3.70	50.5	63.9	< 0.0001	HS

Shoulder ROM was expressed by percentages (%) shoulder in comparison with the contra-lateral (non-involved).

SPADI: Shoulder Pain and Disability Index

Patients in the calcitonin group outperformed the placebo group across all categories, and their progress was noticeably greater than that of the control group. At the post-treatment visit, there was a statistically significant difference between the two groups when it came to shoulder ROM except for that of external rotation.

The difference between the Shoulder Pain and Disability Index (SPADI) score of both groups was highly significant.

7. Subgroup Analysis of comparison between pre and post treatments within each group:

(i) SHOULDER RANGE OF MOTION (ROM) : FLEXION (Table 12)

CONTROL

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
111.55	18.18	75	140	122.76	15.96	75	145	0.0078	VS

INTERVENTION

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
107.41	19.67	75	145	135.69	15.45	105	165	<0.0001	HS

While both group showed improvement in Flexion of shoulder, the data of intervention Group was highly significant statistically.

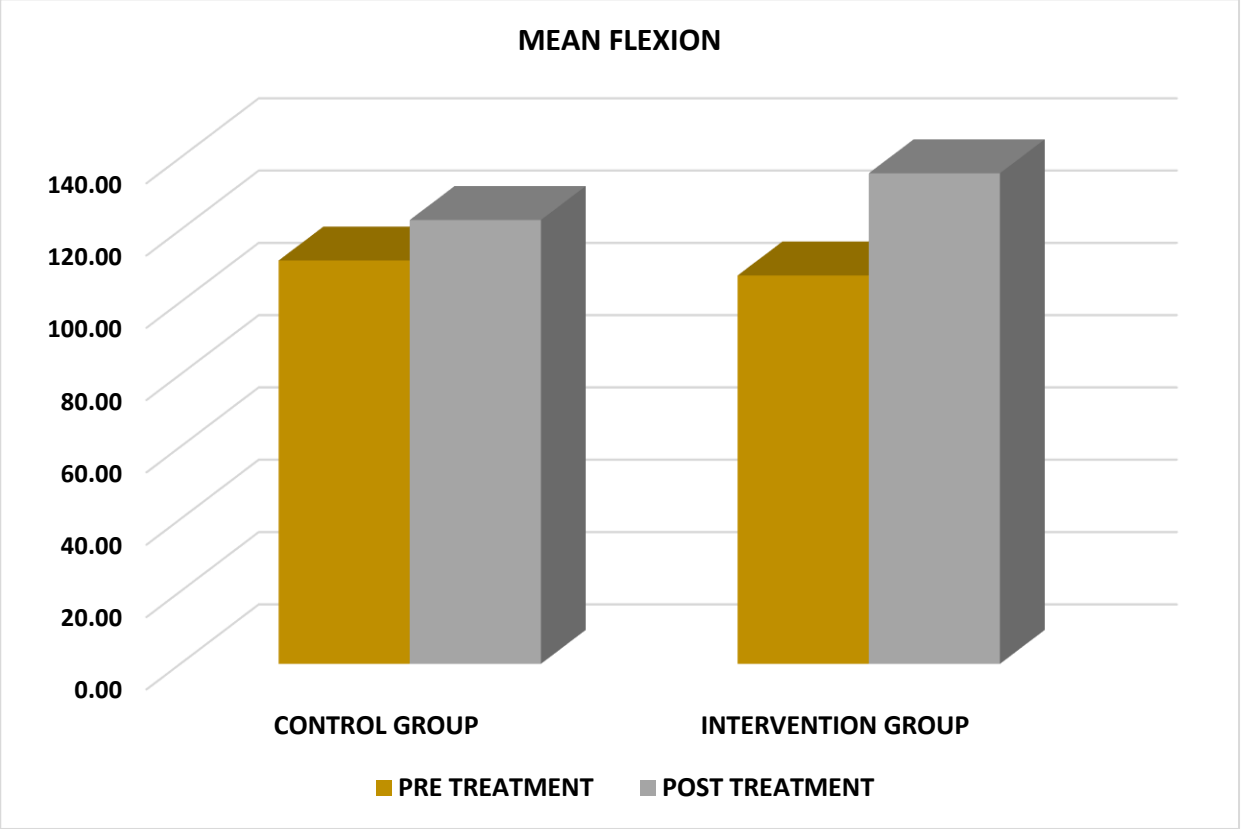

Fig 28 : Mean flexion comparison between both groups

(ii) SHOULDER RANGE OF MOTION: EXTERNAL ROTATION (Table 13)

CONTROL

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
42.07	11.77	20	65	49.31	10.41	25	65	0.0080	VS

INTERVENTION

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
37.59	13.40	5	60	52.69	11.18	25	70	<0.0001	HS

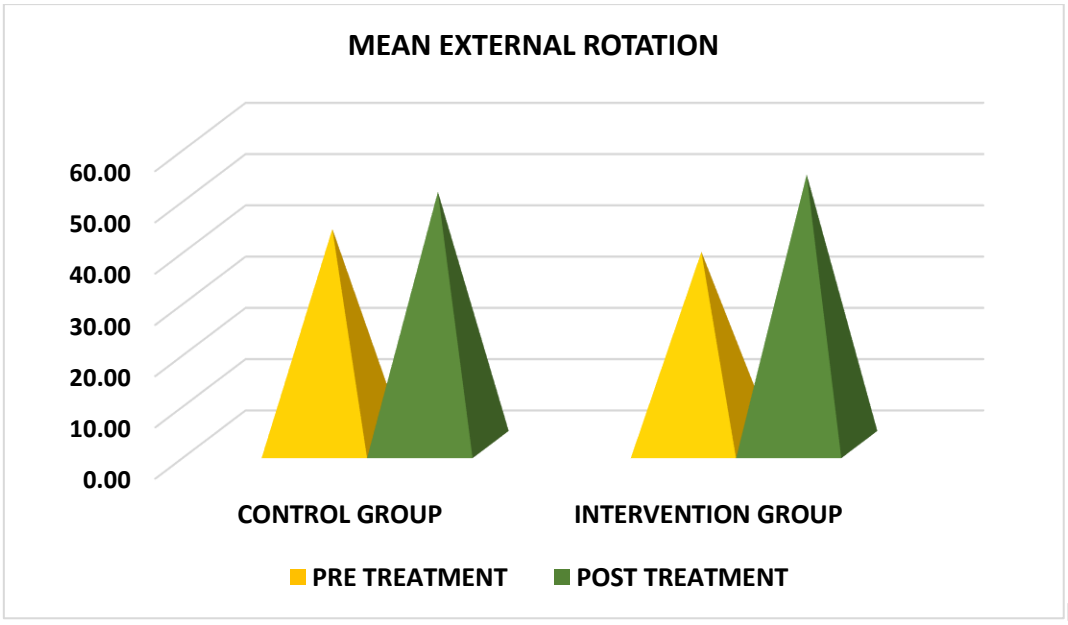

Fig 29 : Mean external rotation comparison between both groups

While both group showed improvement in external rotation of shoulder, the data of intervention Group was highly significant statistically.

(iii) SHOULDER RANGE OF MOTION (ROM) : ABDUCTION (Table 14)

CONTROL

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
96.03	17.18	70	140	105.86	16.15	75	150	0.0144	S

INTERVENTION

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	p VALUE	INFERENCE
98.45	21.13	30	140	126.55	21.68	60	160	<0.0001	HS

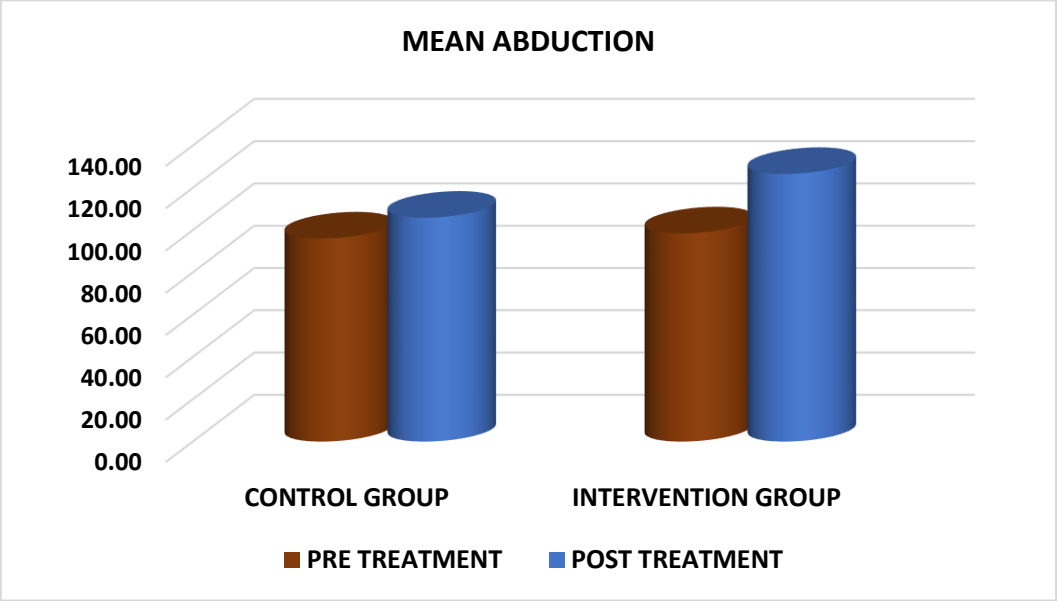

Fig 30 : Mean abduction comparison between both groups

The intervention group had more statistical significance as compared to the control group when it came to improvement in mean abduction range of motion.

(iv) Comparison of Pre and Post treatment Shoulder Pain and Disability Index (SPADI) scores in both groups : (Table 15)

CONTROL

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
84.26	5.31	74.3	94.3	66.04	3.38	59.8	71.9	< 0.0001	HS

INTERVENTION

GROUP

PRE TREATMENT				POST TREATMENT					
MEAN	**S.D.**	**MIN**	**MAX**	**MEAN**	**S.D.**	**MIN**	**MAX**	**p VALUE**	**INFERENCE**
82.20	5.07	71.5	93.2	57.23	3.70	50.5	63.9	<0.0001	HS

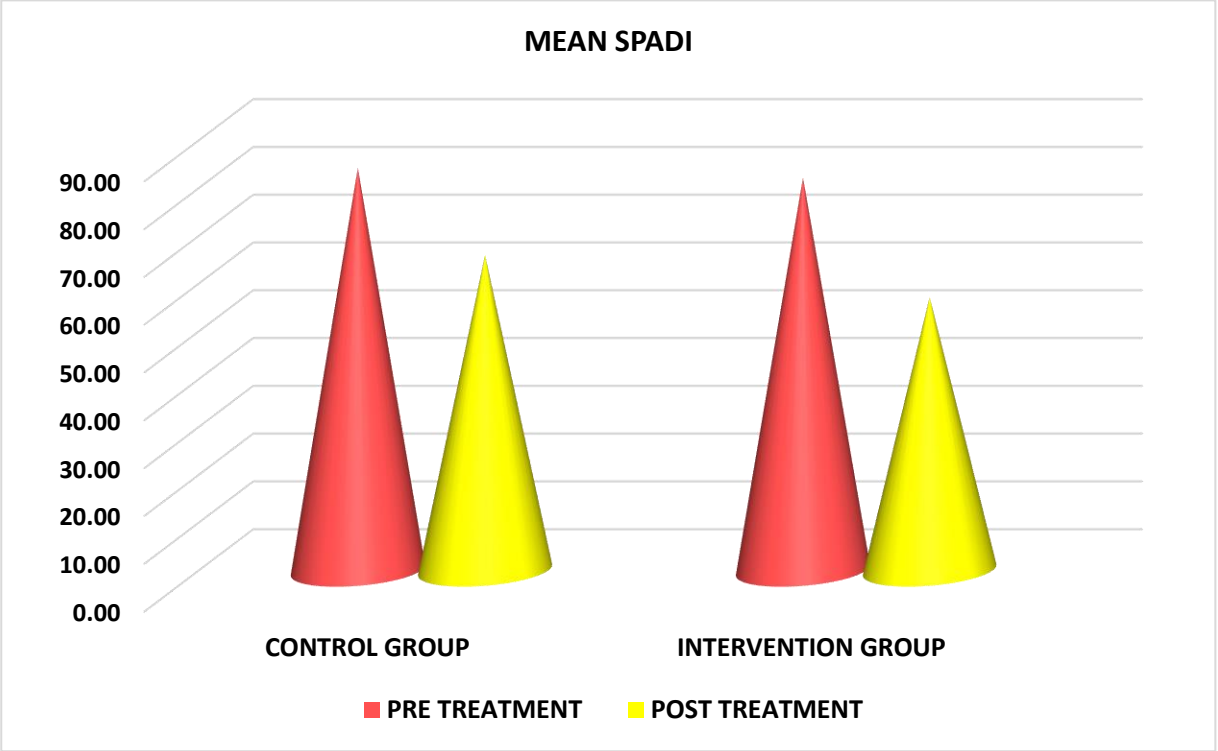

Fig 31 : Comparison of SPADI scores in both groups

SPADI score improvement was noted in both groups, however score improvement was seen more in intervention group. This score difference was statistically significant.

DISCUSSION

Shoulder adhesive capsulitis or frozen shoulder is a disease with unknown pathogenesis. Histochemical studies demonstrated synovial inflammation and reactive fibrosis of articular capsule. Frozen shoulder management has been regarded as a controversy in orthopedics since its description by Codman in 1934. Categorizing the adhesive capsulitis based on clinical examinations and histological features into four stages (painful phase, freezing, frozen and thawing stage) facilitates the treatment selection more efficiently (4, 14). The initial treatment is conservative including physiotherapy and non-steroid anti-inflammatory drugs (NSAIDs). Intra-articular injection of corticosteroids is useful to reduce pain and disability of the patients during painful phase or freezing stages . Manipulation is sometimes used for the resistant cases of frozen shoulder (74). Arthroscopic release of shoulder joint adhesive capsulitis is an effective way of minimizing morbidity of frozen shoulder in its later phase for patients suffering from limited range of motion . Open surgical release of shoulder joint will be finally used in case of failure of the mentioned methods . All mentioned treatment methods are associated with their own special risks and complications, and none of them is regarded as definite and safe treatment. On the other hand, it is difficult to tolerate pain and motion range of shoulder for about 12–18 months since it deprives the patients from their routine life, occupational and recreational activities. Most patients cannot rest due to nocturnal pain .

The prevalence of the disease (2–5 %) (18) especially in diabetic patients as well as more problems of the affected patients restricting their routine activities for at least 12 months makes it necessary to study the problem and find non-invasive treatment ways with easy administration and fewer complications .In a double-blinded clinical trial study, 40 patients with adhesive capsulitis were treated using oral steroid. The treatment significantly affected pain mitigation and improved shoulder ROM (77).

The mechanism of action of calcitonin is not fully understood. In addition to its hypo-calcaemic effect, there are several proposed hypotheses ranging from peripheral to central nociception mechanisms including: serotoninergic or catecholaminergic effect, inhibiting synthesis of the inflammatory mediators,

and provoking the releasing of the endogenous opioid neuropeptides such as endorphins (76 77). The analgesic activity of calcitonin is well established, both through clinical and experimental studies. To evaluate the effect of calcitonin spray in treating Complex regional pain syndrome CRPS in a clinical trial study, Sahin et al. (78) evaluated 35 patients with suffered from CRPS resulting from Orthopedic surgeries using intranasal calcitonin and significant pain mitigation was observed in the calcitonin group.

Appelboom et al. (5) concluded that calcitonin especially in the form of intranasal spray was useful in alleviating pain of the patients suffering from CRPS, Ankylosing spondylitis, arthritis rheumatoid, shoulder adhesive capsulitis, spinal fractures, and metastasis (79).

Waldburger et al. (80) prospectively studied 50 patients suffering from shoulder adhesive capsulitis at three medical centers in Switzerland and concluded that intranasal calcitonin is effective in pain mitigation and shoulder function improvement. Brue et al. investigated the effect of subcutaneous calcitonin combined with physio- therapy for treatment of adhesive capsulitis. Subcutaneous injection of calcitonin along with physiotherapy for 21 days led to promising results. However, it did not affect post-trauma adhesive capsulitis treatment outcomes.

In this present study, out of 58 observed cases, 22 were male and 36 were female. The mean age of the patients was 55± 5 (range 50–59 years). Demographic characteristics were statistically similar between two groups

Patients were evaluated with regard to SPADI scores pre-treatment, and it was revealed that there were no significant differences between the two groups . None of the patients in either group reported any serious side effects during the study duration. There were fewer patients in the calcitonin group with post-treatment nocturnal pain in comparison with the control group

Besides calcitonin spray in intervention group , both groups were administered with similar shoulder physiotherapy and oral NSAIDs. In post-treatment follow-up, the scores of shoulder pain, ROM, and the

patients' functional outcome SPADI were significantly improved in both groups (P <0.0001); it means that both groups had-to some extent- acceptable results. However, there was a statistically difference between two groups considering post-treatment SPADI In all categories, the patients in calcitonin group outrun the placebo group and improv ement in the calcitonin group was significantly more than the placebo one .

There was a statistically significant difference between two groups considering shoulder ROM at post-treatment visit. It means that although patients in both groups bene- fitted from oral NSAIDs and physiotherapy sessions, shoulder ROM in calcitonin group improved more effective.

Post treatment flexion with p value <0.0001 showed Highly significant significant changes compared to post treatment control group with p value <0.0078

Post treatment External rotation in Intervention group with pvalue <0.0001 showed highly significant changes compared to post treatment in Control group with a p value 0.0080

Post treatment Abduction in Intervention group had pvalue <0.0001 which was highly significant compared to Control group with p value 0.0144

The study Results shows that Affected side with pvalue 0.7797 , duration of symptom with pvalue 0.8300 ,Nocturnal Pain (pvalue 0.4013) all were proved statistically not significant.

The secondary objective of the study was to know the risk factors associated with Adhesive Capsulitis such as Diabetes mellitis, Hypertension and Hypothyroidism. All were statistically proved insignificant with pvalue 0.9846 and hence a direct relationship could not be established.

To our knowledge, this study is one of the fewest works on using calcitonin in alleviating pain for adhesive capsulitis (waldberger) and it may be the first one that applied intranasal calcitonin.

According to our findings, utilizing intranasal calcitonin in association with physiotherapy and NSAIDs significantly mitigates the patients' pain intensity, increases shoulder ROM, and improves functional outcome.

The present study results shows that the Intranasal calcitonin application for 6 weeks has significant improvement in reduction in shoulder pain and stiffness and improvement in physical motion and range of motion. It also reduces the requirement of NSAIDs taken by the patient.

The result of this study revealed that Intranasal calcitonin application shows significant changes in the post treatment follow up of the intervention group. This study also observed no adverse effects in any of the 29 subjects. No participants dropped out of the study and the subjects were consistent with the intervention spray. .

Strengths of the study

a) It is a randomized controlled trial
b) Prospective study
c) Double blinded study

Limitations of the study

a) The sample size was relatively smaller.

b) There was no follow-up in this study post 6 week

c) Diurnal variations might have influenced the results.

d) Other physical activities can act as confounding factors for study

Directions for Future Research

a) This study should replicate with lager sample size.

b) A randomized controlled trial with multi arm study could be better for definite conclusion.

c) Strong methodology with follow-up is essential to support our result.

d) Objective variables like digital goniometer; bio-markers for the pain can be used.

e) Multicenter study

CONCLUSION

Frozen shoulder is a common disease which causes significant morbidity. Despite over a hundred years of treating this condition the definition, diagnosis, pathology and most efficacious treatments are still largely unclear. Our study reveals that Intranasal calcitonin was beneficial in the management of shoulder pain, disability index, and shoulder range of motion in patients with Adhesive Capsulitis. This Study also showed that there is no significance in the association of risk factors with Adhesive Capsulitis. Intranasal calcitonin spray could be an additional safe alternative in shoulder adhesive capsulitis.

SUMMARY

Adhesive capsulitis (frozen shoulder) is a common shoulder condition that affects the glenohumeral joint's soft tissue. Signs include painful movement restriction and inability to do everyday chores. Calcitonin is a hormone produced by the Parafollicular C-Cells of the thyroid gland and its efficacy in treatment of painful conditions has been established.

This research intends to investigate the efficacy of calcitonin in treating adhesive capsulitis of the shoulder and its risk factors.

Data was collected from 58 patients who reported to the Orthopedic OPD in KLE'S Dr. Prabhakar Kore Hospital & Medical Research Centre and Charitable Hospital in Belagavi over a period of one year. They were randomized into 2 groups of 29 patients each – intervention group and control group.

The intervention group received intranasal calcitonin for a period of six weeks. Physiotherapy and nonsteroidal anti-inflammatory medications were provided to both, the intervention and the control group. Prior to and after therapy, the patients' shoulder pain and shoulder range of motion were assessed (ROM) using a goniometer and the Shoulder Pain and Disability Index.

Of 58 observed cases, were 22 male and 36 were female. None of the patients in either group reported any serious side effects during the study duration. In post-treatment follow-up, the scores of ROM and SPADI scores were improved in both groups. It means that both groups had-to some extent- acceptable results. However, there was a significant difference between the extent of improvement between the two groups considering shoulder scores (SPADI) and the ROM.

In the intervention group, out of 29 patients given intranasal calcitonin, 25 patients had relief of symptoms. In post treatment follow-up ROM – flexion and extension improvement was statistically significant with p value <0.05. The patients' functional SPADI score improvement was considered to be highly significant

statistically ($p < 0.0001$) in calcitonin group as compared to that of control group. In all categories, the patients in calcitonin group outran the control group and improvement in the calcitonin group was significantly more than the control group. It means that although patients in both groups benefitted from oral NSAIDs and physiotherapy sessions, shoulder ROM and SPADI in calcitonin group improved more effectively.

From this study we can derive that intranasal calcitonin spray increases shoulder ROM, and improves functional outcome in patients suffering from shoulder adhesive capsulitis. Intranasal calcitonin spray could be an additional safe alternative in shoulder adhesive capsulitis.

This study's strength is that it is a double blinder prospective randomized controlled trail, however, the sample size is small and there is no follow up beyond 6 weeks. In the future, a multicentric study with larger sample size and longer follow up will yield better results about the efficacy of calcitonin in shoulder adhesive capsulitis.

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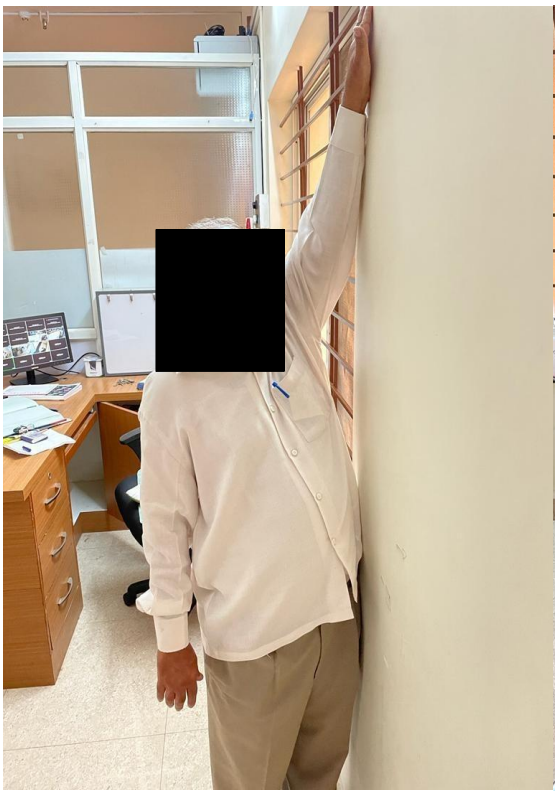
ANNEXURE I

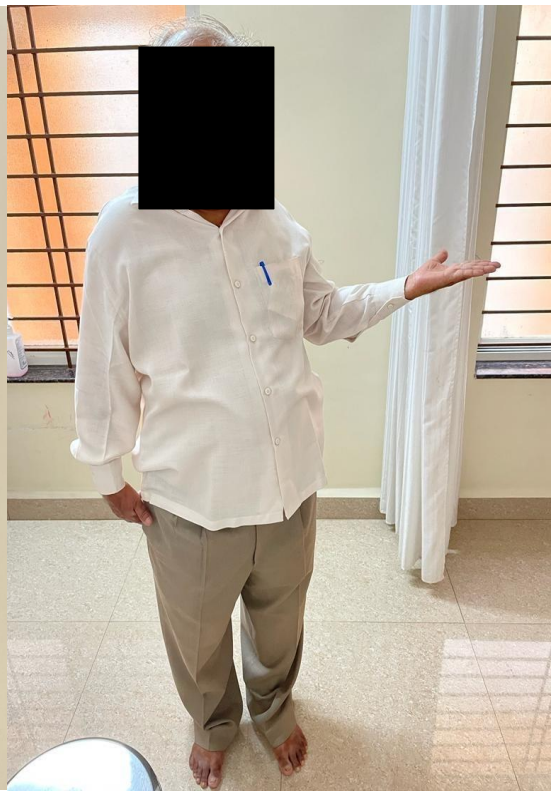
CLINICAL PHOTOS

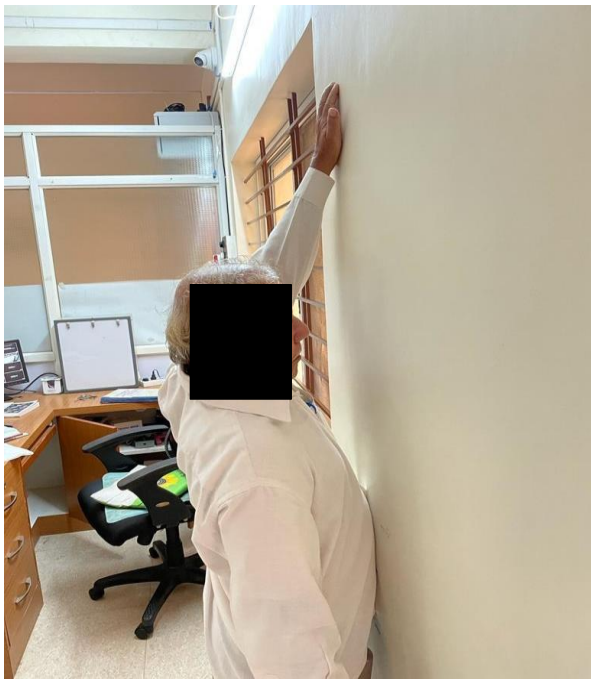
1) INTERVENTION GROUP (Fig 32)

PRE – TREATMENT

6 WEEKS POST TREATMENT WITH CALCITONIN NASAL SPRAY

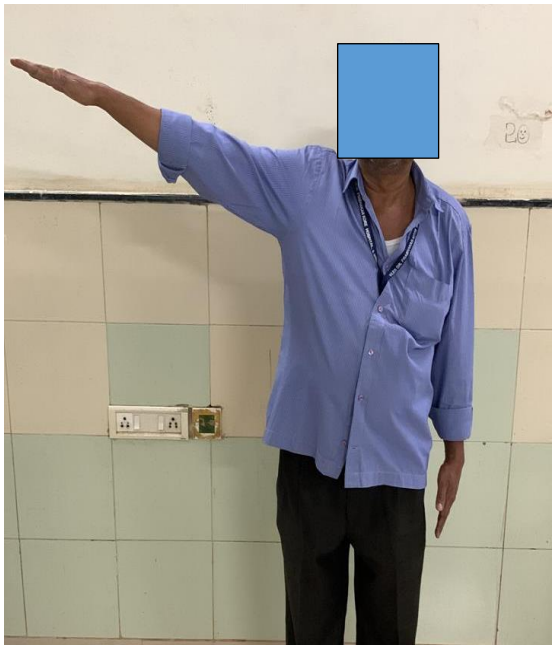






2) CONTROL GROUP (FIG 33)

PRE TREATMENT



6 WEEK FOLLOW UP OF CONTROL GROUP

ANNEXURE II

PROFORMA

"RANDOMIZED CONTROLLED STUDY ON THE EFFECT OF CALCITONIN IN SHOULDER ADHESIVE CAPSULITIS"

PATIENT NO :. IP NO.

AGE: SEX:
ADDRESS:
CHIEF COMPLAINTS:

VISIT 1

PRE TREATMENT

HISTORY

- Age
- Gender
- Occupation
- Weight
- height
- Dominant side
- Involved site
- H/o shoulder trauma
- H/o of prior shoulder surgery
- H/o shoulder pain related treatment
- Duration of frozen shoulder
- Nocturnal pain
- H/o systemic diseases
- ROM in flexion, extension and external rotation

RELEVANT INVESTIGATIONS:

- Blood: CBC, ESR
- RBS
- Serum Calcium
- Serum Creatinine,
- Serum Total Cholesterol
- SGPT

DIAGNOSIS:

- X-ray of affected Shoulder joint AP VIEW

Range of movement of Shoulder joint at

- Flexion
- External Rotation
- Abduction.

Shoulder functional outcome

- SPADI

VISIT 2

6 WEEKS FOLLOW UP

Range of movement of Shoulder joint at

- Flexion
- External Rotation
- Abduction

Shoulder functional outcome

- SPADI

COMPLICATION:

ANNEXURE III

INFORMED CONSENT FOR THE STUDY

TITLE OF THE STUDY: "Prospective Randomized controlled trial on the effect of calcitonin in Shoulder Adhesive capsulitis"

PRINCIPAL INVESTIGATOR:
Associate Professor, Department of Orthopaedics,
J.N. Medical College, K.A.H.E.R, Belagavi, Karnataka.

This Informed Consent Form is for men and women who attend Dr PRABHAKAR KORE HOSPITAL AND RESEARCH CENTRE and who we are inviting to participate in Randomised controlled trial on adjunctive system to treat Shoulder Adhesive Capsulitis

The title of The Randomised controlled trial is "EFFECT OF CALCITONIN IN TREATING SHOULDER ADHESIVE CAPSULITIS."

Name of Principal Investigator:

This Informed Consent Form has two parts:

• Information Sheet (to share information about the research with you)

• Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction:

I, PG Resident, JAWAHARLAL NEHRU MEDICAL COLLEGE, Belagavi. We are doing Randomized controlled trial on the effect of calcitonin in treating shoulder Adhesive Capsulitis, which is very common in this country. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you

will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Purpose of the research:

Adhesive capsulitis is a common shoulder disease with prevalence rate of 2–10 % in outpatients of orthopaedic, rheumatologic, and physiotherapy clinics.

Although much work has been done to treat the disease, the results of non-operative treatment of the adhesive capsulitis are not satisfactory.

Calcitonin has been recognized by its role in maintaining calcium balance including inhibition of osteoclast activity. Calcitonin has been found to inhibit frozen shoulder fibrosis related molecule expression and cell adhesion by synovial capsular fibroblasts.

Very few publications are available on effect calcitonin in shoulder adhesive capsulitis, proper randomised controlled trial is the need of the hour.

Participant selection

Adults with Age more than 40years and less than 70 years, who are Cases of adhesive capsulitis ie shoulder pain with reduced range of motion

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at

this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offer the treatment that is routinely offered in this clinic/hospital for adhesive capsulitis, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

A one-year hospital based Randomized controlled study. Patients diagnosed with adhesive capsulitis will be divided into 2 groups, the intervention group and control group. The intervention group will receive nasal calcitonin 200 units/day for 6 weeks along with physiotherapy and NSAIDs.The control group will be receiving only physiotherapy and NSAIDS. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results.

The Principal investigator will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

B. Description of the Process:

Nasal calcitonin will be given 200 units along with home based Physiotherapy and NSAIDS , followed by follow up 6weeks post treatment.

We will also ask you a few questions about your general health and measure in the form of questionnaire.

Duration

This is a 6-week Randomized controlled study.

Risks

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you are getting and make changes.

Benefits

There may not be any benefit for you but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

Reimbursements

You will not be given any other money or gifts to take part in this research

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone.

Sharing the Data and results

The knowledge that we get from doing this research will be shared with you through journal publications. Confidential data & information will not be shared.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the centre/institute/hospital.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. This proposal has been reviewed and approved by (ETHICS COMMITTEE JNMC, Belagavi), which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact (name, address, telephone number.)).

PART II: Certificate of Consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign. A researcher or the person going over the informed consent must sign each consent. The

certificate of consent should avoid statements that have "I understand...." phrases. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____ Day/month/year

If illiterate

Aliterate witness must sign (if possible, this person should be selected by the participant and should have no connection to-the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, andthe individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____

Thumb print of participant

Signature of witness _____

Date _____ Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____ Day/month/year

VOLUNTARY PARTICIPATION / WITHDRAWAL:

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part, I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other services that I receive. The investigator or the sponsor may stop my participation in this study. I will tell of any important new findings that may

change my willingness to continue to take part. If I choose not to take part in the study, I will receive the standard treatment for patients with my condition.

COMPENSATION:

As the subject voluntarily consents to be a part of the study, no compensation will be given.

CONFIDENTIALITY:

All information collected about the subject during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify the subject in this research record. Information from this study may be presented but the subjects identify will be confidential in any publication.

If any enquiries in the future or in case of study related injury or illness, you may contact following person:

Post-graduate resident,
Department of Orthopaedics,
J.N. Medical College,
K.A.H.E.R, Belagavi 10.
Ph. No. 6282009742.

Associate Professor
Dept of Orthopaedics,
J.N. Medical College,
K.A.H.E.R, Belagavi10
Ph. No. 9844333082

ANNEXURE IV

MASTER CHART

A) CONTROL GROUP

Patient No	Age	Sex	Dominant Side	Affected side	Duration of sympto	Nocturnal pain	Systemic disease	S. Calcium	RBS	Pre Treatment				Post Treatment (at 6 weeks)			
										Flexion	Ext Rotation	Abduction	SPADI	Flexion	Ext Rotation	Abduction	SPADI
1	62	F	RIGHT	RIGHT	2	Y	DM	9.8	145	130	40	90	83	140	45	95	64.5
2	63	F	RIGHT	RIGHT	4	N		8.8	109	115	45	120	84.3	125	55	130	69.2
3	50	M	RIGHT	LEFT	5	y	HTN DM	9.1	170	85	25	70	90.1	105	30	90	70.9
4	52	M	LEFT	LEFT	1	N	DM	8.8	164	120	35	90	84.6	125	40	90	67.2
5	61	F	RIGHT	RIGHT	8	N		9	103	140	45	110	80.7	140	50	125	61.7
6	56	M	RIGHT	RIGHT	7	Y	DM	9.5	162	115	40	125	77	120	40	125	68.8
7	53	F	LEFT	LEFT	3	Y		8.8	125	120	55	100	81.2	130	60	110	63.6
8	49	M	RIGHT	RIGHT	2	N	HYPOTHYROIDISM	9.5	117	110	50	80	87	135	60	85	65.9
9	55	F	RIGHT	RIGHT	5	Y		7.7	132	100	30	90	85.4	125	45	105	68
10	61	F	LEFT	LEFT	7	Y	HTN DM	10	159	120	40	100	82	140	55	115	62.7
11	60	M	RIGHT	LEFT	4	y	HTN DM	10.1	198	130	60	110	77.2	140	60	110	64.7
12	69	F	RIGHT	RIGHT	4	Y		9.4	127	80	25	90	92.1	100	35	105	70.5
13	49	F	RIGHT	RIGHT	5	y	DM	8.7	180	95	35	70	89.4	115	45	95	69.6
14	51	M	RIGHT	LEFT	6	Y		8.5	111	100	50	80	85	115	60	95	68.7
15	54	M	LEFT	LEFT	7	Y	HTN	8.8	109	105	40	75	85.4	110	45	75	67.7
16	57	F	RIGHT	RIGHT	5	Y		9.7	122	90	45	70	92.3	110	55	90	71.8
17	63	F	RIGHT	RIGHT	3	Y	DM	9.3	221	125	55	80	84.3	130	55	90	63.3
18	65	F	RIGHT	RIGHT	5	N		8.8	109	115	50	95	87.2	125	55	105	64.8
19	55	F	RIGHT	LEFT	4	Y	DM	9.5	154	130	55	110	76.2	130	60	115	65.3
20	52	M	RIGHT	RIGHT	2	N		8.9	119	125	40	95	79.4	135	45	110	61.6

21	59	M	LEFT	RIGHT	5	Y	DM	9.2	132	85	20	90	88.4	95	25	90	68.6
22	65	F	RIGHT	LEFT	6	N		9.7	117	75	25	95	94.3	75	35	100	71.9
23	62	F	RIGHT	RIGHT	2	Y		8.6	115	105	45	90	85.2	120	55	105	64.7
24	57	M	RIGHT	RIGHT	2	N		8.2	85	140	60	120	75.4	145	65	120	59.8
25	61	F	RIGHT	RIGHT	4	Y	DM	9	143	115	45	100	81.9	125	50	110	65.8
26	55	M	RIGHT	RIGHT	1	Y	DM	9.8	176	110	35	90	83.4	120	45	95	66.7
27	57	F	RIGHT	LEFT	3	Y		9.2	92	120	40	110	84.6	135	55	115	62.8
28	64	F	RIGHT	RIGHT	5	Y	DM	8.6	171	95	25	100	92.1	110	40	125	63.7
29	60	F	RIGHT	RIGHT	2	Y	DM	8.7	196	140	65	140	74.3	140	65	150	60.6

B) INTERVENTION GROUP

Patient No	Age	Sex	Dominant Side	Affected side	Duration of symptoms	Nocturnal pain	Systemic disease	S. Calcium	RBS	Pre Treatment				Post Treatment (at 6 weeks)			
										Flexion	Ext Rotation	Abduction	SPADI	Flexion	Ext Rotation	Abduction	SPADI
1	47	M	Right	Right	4	Y		9	85	110	20	70	83	150	40	90	52.3
2	60	f	Right	Left	1	Y	DM	9.5	168	110	40	100	71.5	140	50	130	58
3	50	M	Right	Right	3	N	DM	9.7	110	80	5	30	81	110	25	60	60.2
4	54	F	right	right	2	y	htn	8.8	120	130	30	75	86.1	150	48	140	56.8
5	57	m	left	left	5	y	dm	9.1	137	90	45	80	93.2	125	58	120	57.7
6	59	f	right	right	6	y		8.1	90	100	55	110	78.5	130	65	115	58.3
7	67	m	right	right	1	n	dm,htn	7.6	100	110	45	90	82.9	145	65	130	54.8
8	49	m	left	right	7	n		9.1	140	135	35	95	90.2	155	55	155	57.7
9	53	f	right	left	4	y	htn	9.7	110	110	50	120	88.4	140	55	135	51.9
10	59	f	right	right	5	n	dm	8.1	95	90	55	100	86.9	125	50	130	57.8
11	61	f	right	left	3	y		7.9	127	125	35	110	80.2	145	45	145	53.9
12	64	m	right	left	1	y	dm	8.9	172	145	45	140	90	165	50	160	56.9
13	44	f	right	right	2	y		9.1	120	95	40	110	86.2	135	55	125	54.9
14	50	f	right	right	6	n	hypothyroidism	8.4	95	115	25	95	77.4	160	45	155	55.9
15	59	m	right	right	4	y	dm	9.6	190	85	15	85	84.2	130	30	135	58.9
16	62	f	right	left	5	y		9.1	110	85	45	95	81.7	115	65	125	61.7
17	47	f	right	right	3	y		9	116	75	30	80	81.9	105	55	110	62.8
18	51	f	right	right	5	n		7.9	146	130	55	120	83.2	140	70	125	63.9
19	59	m	right	left	4	n	dm	8.9	176	120	60	110	85.2	135	60	130	61.9
20	56	m	right	left	6	y	dm,htn	8.6	156	105	40	115	76.3	125	55	125	62.9
21	48	m	left	right	2	y	htn,DM	9.2	220	110	50	105	75.8	140	65	155	56.9
22	58	f	right	right	4	n		9.5	118	100	40	90	85.8	135	45	110	56.9

23	61	f	right	right	5	y	DM	9.1	189	110	25	95	76.9	130	45	100	59.8
24	47	f	right	right	7	n		8.8	136	95	35	105	77.4	115	40	115	61.9
25	52	f	left	left	4	y	dm	7.7	224	135	20	125	80.1	145	65	145	51
26	49	m	right	right	3	y		8.7	110	145	30	130	76.7	160	70	155	50.5
27	57	f	right	right	3	n		9.1	128	80	30	90	81.4	115	50	110	52.9
28	59	f	right	right	5	n	dm	9.3	176	90	35	90	76.8	125	45	115	56.8
29	60	f	right	right	6	y	dm	8.9	197	105	55	95	84.8	145	62	125	53.8

ANNEXURE V

RANDOMIZATION CHART

INTERVENTION GROUP	CONTROL GROUP	
1	2	
3	5	
4	7	
6	12	
8	15	
9	18	
10	19	
11	21	
13	24	
14	26	
16	28	
17	31	
20	32	
22	34	
23	37	
25	38	
27	40	
29	41	
30	43	
33	44	
35	46	=
36	47	
39	49	
42	50	
45	52	
48	53	
51	54	
55	56	
57	58	
60	59	