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Diclofenac with Heparin topical gel for soft tissue injuries

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Objective: To evaluate the efficacy and safety of topical Diclofenac with Heparin (Diclofenac sodium 1% and Heparin 200 IU w/w) gel in subjects with acute blunt and soft tissue injuries. Design: Open labelled, non-comparative multicenter study. Setting: 25 study centers in India. Participants: 296 patients with acute blunt and soft tissue injuries like sports injury, sprain and strain, frozen shoulder and knee pain. Interventions: Diclofenac with Heparin topical gel was applied t.i.d. for ≥48 hours up to 7 days.

Introduction-

Historically NSAIDs have been used to assist the resolution of pain in conditions of OA of the knee and sports and soft tissue injuries. A major drawback of using oral forms of NSAIDs such as diclofenac is the high incidence of major adverse effects such as gastrointestinal bleeding, gastric ulceration and renal disease implications. The use of topical formulations of diclofenac is thought to be as efficacious as oral formulations without the risk of systemic side effects. Topical diclofenac is thought to reduce inflammation via inhibition of the COX 2 isoenzyme. This review addresses the current evidence of the efficacy of topical formulations of diclofenac for treatment of OA of the knee and soft tissue and sports injury. Overview Musculoskeletal conditions range from intra articular disorders such as rheumatoid arthritis and osteoarthritis, injuries that involve simple ligaments such as sprains and extra articular joint disorders such as fibromyalgia and myofascial pain. In the UK, ankle sprains are a common soft tissue injury and occur in 53 per 10,000 population .By comparison osteoarthritis (OA) is a common joint disorder. Although radiographic evidence of OA is common in persons aged 65 years and over often the severity of symptoms does not correlate well with pathogenic alterations viewed radiographically.

The knee joint is a common site for the development of OA. Up to 11% of older people present with relevant clinical symptoms of OA of the knee along with variable forms of disability and long–term pain that requires symptom management. It is postulated that OA will become a global cause of disability in patients by the year 2020. OA is generally thought of as a disorder of middle–aged and older people.

Commonly affected sites include: hip, knee and spine. Typical symptoms include: joint pain in and around the joint site, morning stiffness lasting up to 30 minutes, loss of function, immobility and joint instability. Onset of symptoms is insidious. Pain is generally worse during motion and can be alleviated by rest. Patients with OA of the knee may complain of alterations to the gait and often experience a variety of forms of pain varying from a sharp pain to a dull constant ache. Pain is a complex sensory process which is related to specific tissue damage. During trauma to the skin, blood vessels release inflammatory mediators such as prostaglandins, neuropeptides such as substance P and calictonin-gene related peptide.

These substances act as a stimulus and cause peripheral nociceptor C and Aδ fibers to depolarize. This leads to the transmission of signals (signal transduction) via the dorsal horn to the cerebrum. During inflammation there is a hyperresponsive response whereby signal transmission to the dorsal horn does not require a stimulus. The hyperresponsive response can be controlled by NSAIDs . In OA of the knee the diagnostic classification criteria include: knee pain and osteophytes on X ray and at least one of the following: crepitus (irregularity of opposing cartilage surfaces) on motion, morning stiffness lasting 30 minutes and age over 50 years.

These additional characteristics are required because pathogenic changes on X ray may occur without the patient demonstrating symptoms of pain. The pathogenesis of OA is illustrated by degenerative changes to the articular cartilage of joints, new bone or osteophyte formation, loss of joint space between bone endings and sclerotic alterations to subchrondral bone. With the erosion of the articular cartilage, nociceptors become sensitized leading to chronic pain. Pain can result from the stretching of the adjacent periosteum, growth of osteophytes, presence of microfractures, intraosseous pressure and synovitis. The involvement of peri-articular tissues can also lead to joint pain, limitations in movement and disability. Pain can arise from numerous sites; subchrondral bone, periosteum, joint capsule, synovial membrane, peri-articular muscles and ligaments. Numerous cytokines have been implicated in the pathogenesis of OA. Interleukin -1 tumour necrosis factor þ are thought to activate enzymes associated with the proteolytic digestion of cartilage . Insulin growth factor 1 and tissue growth factor þ may be involved in cartilage synthesis and repair processes .

OA develops when cartilage catabolism exceeds the process of cartilage synthesis. The cartilage catabolic process is maintained by several collagenolytic enzymes: • Fibroblast collagenase 1 or matrix metalloproteinase -1 • Neutrophil collagenase2 or matrix metalloproteinase -2 • Collagenase 3. Treatment options include non-pharmacological and pharmacological approaches. Non-pharmacological approaches include weight reduction, exercise, patient education and joint support. Pharmacological approaches include the use of regular analgesics such as paracetamol to control pain and symptoms, if joint effusion is present patients may need intra-articular injections of corticosteroids. For uncontrolled pain and symptom control the recent EULAR recommendations suggest that Non Steroidal Anti-Inflammatory Drugs (NSAIDs) can be used as apart of pain management or patients with OA of the knee.

NSAIDs can also be used to manage peri-articular and extra articular joint disorders such as tendinopathies and could also be used to treat fibromyalgia [16]. A drawback of using NSAIDs is the severity of side effects affecting the gastrointestinal tract, renal complications and cardiotoxicity. Topical NSAIDs are postulated to produce fewer side effects especially cardiac related effects and better tolerability [17] as they are able to reach the target site either via cutaneous

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penetration or systemic delivery [18]. Cutaneous delivery refers to the delivery of a drug to the site of application where the drug is able to target the peripheral nerves and soft tissues local to the site of application [19]. Although many reports indicate the benefits and efficacy of topical NSAIDs as anti-inflammatory agents and analgesics, these benefits are contested [20, 21]. Chemistry and pharmacokinetics properties Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) and is a weak organic acids (pKa = 4.00).

Although this chemical attribute helps the drug to accumulate in inflammed tissues and improves their effectiveness as anti-inflammatory agents [22] a number of formulations have been developed to improve cutaneous absorption.

Main Outcome Measures: The efficacy assessment of treatment was done based on the overall symptoms of soft tissue injury. The efficacy parameters for this evaluation are: pain of movement (POM), inflammation, haematoma, pain on leaning of injured limb, oedema, swelling, redness and overall pain. A 3-point scoring data was obtained for all these efficacy parameters for Baseline (BL) and End of therapy (EOT), where 0 indicates no symptoms and 3 indicates severe symptoms. Statistical Analysis: Non-parametric Wilcoxon signed-rank test was applied on the data of difference between BL and EOT symptoms scores.

Results or Clinical Course: Patients treated with topical Diclofenac and Heparin gel experienced significantly greater reduction in POM at EOT ($p<.0001$). For all injury cases, there was a significant difference at 5% level of significance ($p < 0.05$), which gives evidence that there is a significant decrease in the symptoms of soft tissue injury for all the efficacy parameters.

Conclusions: Diclofenac with Heparin topical gel applied 3 times daily was a safe and highly effective treatment for the symptoms of blunt and soft tissue injuries, and it could represent a new option for the treatment of acute blunt trauma and other soft tissue injuries. Review of published literature on topical nonsteroidal anti-inflammatory drugs (NSAIDs), diclofenac, and DETP in patients with acute soft tissue injuries was included. Relevant literature was identified on MEDLINE using the search terms topical NSAIDs, diclofenac, diclofenac epolamine, acute pain, sports injury, soft tissue injury, strain, sprain, and contusion, and from citations in retrieved articles covering the years 1978-2008. Review of published, randomized clinical trials and meta-analyses shows that topical NSAIDs are significantly more effective than placebo in relieving acute pain; the pooled average relative benefit was 1.7 (95% confidence interval, 1.5-1.9). In a limited number of comparisons, topical and oral NSAIDs provided comparable pain relief, but the use of topical agents produced lower plasma drug concentrations and fewer systemic adverse events (AEs).

The physical-chemical properties of diclofenac epolamine make it well suited for topical use. In patients with acute soft tissue injuries treated with DETP, clinical data report an analgesic benefit within hours of the first application, and significant pain relief relative to placebo within 3 days. Moreover, DETP displayed tolerability comparable with placebo; the most common AEs were pruritus and other application site reactions. Review of published literature suggests that DETP is generally safe and well tolerated, clinically efficacious, and a rational treatment option for patients experiencing acute pain associated with strains, sprains, and contusions, and other localized painful conditions.