Title: Relative therapeutic efficacy of ketoprofen iontophoresis and transcutaneous electrical nerve stimulation in the management of osteoarthritic knee pains: a pilot study

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Abstract

Background: Osteoarthritis (OA), also known as degenerative joint disease, has no curative treatment. However, pharmacological therapies such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and more recently etodolac (iodine) are commonly used in its treatment. Non-pharmacological therapy, predominantly physiotherapy, is also employed in the treatment of OA.

Objective: This research was aimed at determining the relative therapeutic effectiveness of ketoprofen iontophoresis and transcutaneous electrical nerve stimulation in the management of osteoarthritic knee pain.

Methods: Twenty subjects with diagnosis of OA of the knee joint were randomly selected into the ketoprofen iontophoresis group and the transcutaneous electrical nerve stimulation group. Both groups received quadriceps strength training in addition to their group therapy. Each subject, who had 3 sessions per week over a four-week period, had a total of 12 treatment sessions. Each treatment session lasted 45 minutes.

Results: There was a statistically significant decrease in pain intensity and increase in range of motion in both groups but no significant difference in change in both outcome measures between the groups.

Conclusion: Management of OA of the knee using either ketoprofen iontophoresis or transcutaneous electrical nerve stimulation in addition to quadriceps strengthening exercises in this pilot study was shown to be effective in pain reduction and to increase range of motion. Neither of the interventions was superior. Future studies using a larger sample size are needed to confirm our findings.

Keywords: Ketoprofen iontophoresis, TENS, Osteoarthritis, and Quadriceps strengthening exercise.

Introduction

Osteoarthritis (OA), the most common type of joint disease (Cotran, Kumar, and Collins, 1999), is usually accompanied by focal destruction of articular cartilage lining the synovial joints, plus extensive subchondral bone remodeling and possible bone necrosis (Nguyen and Marks, 2000).

OA is a progressive degenerative joint disease that initially affects joint soft tissue with subsequent involvement of the underlying bone and inflammation of the contiguous synovium (Herfindal and Gourley, 1996). It is also considered to be an intrinsic disease of cartilage in which biomechanical and metabolic alterations result in its breakdown (Cotran, Kumar, and Collins, 1999).

Joints commonly affected by OA include the knees, hips, shoulders, spine, and the interphalangeal joints of the hand and feet, with the knee being the most commonly afflicted (Adedoyin et al. 2002). Ninety percent of the cases of OA of the knee are associated with varus deformity (Hughes, Benson, and Colton, 1987). OA does not show a predilection for a particular race, geographical area, climate, or socio-economic class (Herfindal and Gorley, 1992). Gender differences are said to exist in OA of the knee with male incidence greater before 45 years of age and female incidence greater after 45 years of age (Hartz et al., 1986). About 80 to 90 percent of individuals of both sexes have evidence of OA on reaching 65 years of age (Cotran, Kumar, and Collins, 1999)
The presenting symptoms in patients with OA of the knee include pain, muscle spasm, muscle atrophy, joint stiffness, knee locking, crepitus, and joint enlargement. Function may also be impaired over time, and considerable disability may result. Pain, however, tends to be the major complaint that prompts patients to go to the hospital (Adedoyin et al. 2002).

No curative treatment has yet been found for the treatment of OA (Grimmer, 1992; Nguyen and Marks, 2002), however, pharmacological therapies such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and more recently, etodolac (iodine), are commonly used. NSAIDs, which include piroxicam, ibuprofen, ketoprofen, and diclofenac sodium, remain the main pharmacological management for OA (Schnitzer, 1993). However, there are an estimated 3000 – 4000 deaths recorded each year due to NSAID-related side effects in the United Kingdom and 700 deaths with 7000 hospitalization per year in the United States of America (Drug Bulletin, 1998). An alternative way of delivering NSAIDs into the tissue is through iontophoresis.
Topical forms of NSAIDs, such as ketoprofen, can be delivered into the tissue transdermally. As a result, gastrointestinal side effects related to NSAIDs when taken orally are avoided. Transdermal delivery can further be enhanced by iontophoresis, which is the movement of ions across a biological membrane by means of an electrical current for therapeutic purposes (Low and Reed, 1990). The principle of iontophoresis is based on the repulsion of ions by a similarly charged electrode (Hayes 1979).
Other non-pharmacological interventions for the management of OA include physical therapy (Marks and Cantin, 1997) and in rare cases, surgery (Russel et al., 2000). Physiotherapeutic management commonly advocated for treating the symptoms of OA of

the knee include therapeutic exercises, cryotherapy, and a variety of electrotherapeutic modalities, which includes transcutaneous electrical nerve stimulator (TENS). Operating primarily on the Pain Gate control theory by Melzack and Wall (1965), TENS has become a popular modality in the management of pain. TENS is the application of a pulsed square wave electrical current through surface electrodes placed on the skin to the peripheral nerve fiber for the control of pain (Akinbo, 1997). It is non-invasive, non-toxic and relatively free from side effects (Roche and Wright, 1990).

The effectiveness of the use of TENS in the management of OA remains controversial (Aubin and Marks, 1995). Akinbo (1997) reported beneficial effects while other studies have not found any benefits. This research aims at determining the relative therapeutic effectiveness of ketoprofen iontophoresis versus TENS in addition to quadriceps strengthening exercises (QSEs) in the management of osteoarthritic knee pain. We hypothesized that there would be no significant difference in pain relief by the use of ketoprofen iontophoresis (KI) or TENS in addition to QSEs in the management of OA of the knee. Also, there would be no significant difference in the increase in range of motion (ROM), after KI or TENS in addition to QSEs in the management of OA of the knee.

Methods

Participants
Twenty subjects comprising 13 (65%) females and 7 (35%) males with diagnosis of OA of the knee who were freshly referred to the physiotherapy departments of National Orthopaedic Hospital (NOH) Dala, Kano and Aminu Kano Teaching Hospital (AKTH) were recruited for this study. The subjects were systematically and alternately assigned to the KI group and TENS group as they presented at the departments with the first subject in the KI group, the second in the TENS group and so forth. Inclusion criteria were (i) radiographic evidence of OA of the knee joint and presentation with obvious clinical features of OA described earlier, (ii) ability to independently walk and able to attend an outpatient clinic, and (iii) never received physiotherapy for the management of their OA. The exclusion criteria were (i) pain in the knee joint for reasons other than OA, (ii) cuts and abrasions around the knee joint, (iii) intra-articular injection to the knee, (iv) metallic implant in or around the knee joint, (v) OA secondary to infectious disease or obvious neurological abnormality, (vi) currently receiving oral medication for the treatment of the OA and (vii) current use of a cardiac pacemaker.
Protocols Electrical stimulator: Mcintosh model 5200 portable wall plate, manufactured by Godfrey, 1633N, Halstead St. Chicago. Transcutaneous Electrical Nerve stimulator: dual channel Dana Touch TENS model number, SW – 803. Ketoprofen (Ketonal) gel: Manufactured by Lek Pharmaceutical and Chemical Company, Verovskora 57, Ijubljana Slovenia. Goniometer, visual analogue scale, 5kg sand bags, aquasonic gel, lint pad, water, straps, couch, pillow, and methylated spirit.
Written consent was obtained from all subjects using an institution approved form following a thorough explanation of the study procedures.
A total of 12 treatment sessions were administered to each subject over 4 weeks (3 sessions per week). The same KI treatment protocol was administered for the KI group in both hospitals while the same TENS treatment protocol was administered for the TENS

group in both hospitals on different days by the same physiotherapist. The KI group received KI and QSEs while the TENS group received TENS and QSEs for the management of OA.

KI Group: Following adequate patient and machine preparation, the ketoprofen gel was carefully pasted on the medial aspect of the knee and covered with a lint-padded electrode that was connected to the active terminal of the stimulator. The indifferent electrode was soaked in water and placed over the lateral aspect of the knee with the 2 electrodes held in place with a strap. A direct current of 4MA was then applied for 15minutes (Sorinola and Ogunfunwa, 2000). The same procedure was then repeated for 15 minutes with the ketoprofen gel placed on the lateral aspect of the knee and connected to the active terminal of the stimulator and indifferent electrode on the medial aspect of the knee.

The patient was then subjected to QSEs similar to that of Marks, Harle, and Wessel (1991), which were carried out in a sitting position with the back supported and upper limb flexed across the upper abdomen. Ten isotonic warm up contractions of the quadriceps were carried out through available pain free range of knee extension at a gentle speed, which was followed by 6 maximal isometric contractions with 5 kg weight in 3 sets of 5 seconds each with an interval of 30 seconds between sets. The exercise period lasted for 15 minutes.

TENS Group: Following adequate preparation of the machine and patient, the TENS electrode was placed on the medial and lateral aspect of the knee following initial application of aquasonic gel on the electrodes. A frequency of 100Hz and a pulse width of 100μS with intensity set according to the subject tolerance for a maximum of 30 minutes (Aubin and Marks, 1995). This was then followed by QSEs as done in KI group.

Data analysis

A 10 cm visual analogue scale (VAS) with 0 being no pain and 10 for excruciating pain was used to assess the pain intensities (Taylor, Hallel, and Flaherly, 1981). These were recorded before the commencement of the treatment program (pretreatment pain intensity) and immediately after subsequent treatment (post treatment pain intensities). The range of pain-free flexion of the knee joint was measured before the commencement of the treatment sessions and after the last treatment session with a goniometer.

The data were analyzed using descriptive statistics of mean, median, standard deviation and inferential statistics of the Student -test. The relationship between pain and range of motion was determined using the Pearson product moment correlation.

Results

Table 1: Characteristics of subjects in both groups

Variable	KI (n = 10)	TENS (n = 10)	Significance
Age (yrs)	55.4±6.1	57.3±6.0	NS
GenderM/F	3/7	4/6	NS
Weight (kg)	69.3±9.6	68.7±9.9	NS

Key: KI = ketoprofen Iontophoresis group; TENS = Transcutaneous Electrical Nerve Stimulation group; NS = not significant

The physical characteristics of the subjects in both groups are presented in Table 1.

In comparing pre- and post-treatment pain intensities in both KI and TENS groups, there was a statistically significant decrease in pain intensities ($t = 14.32$ at $p < 0.001$) and ($t = 12.83$ at $p< 0.001$), respectively. Similarly, comparing pre- and post-treatment ROM in the KI and TENS groups also produced a statistically significant increase in ROM ($t = 6.71$ at $p < 0.001$) in the KI group and ($t = 6.05$ at $p < 0.001$) in the TENS group as seen in Table 2.

Table 2: Comparison of pre- and post-treatment pain intensities and ROM values in KI and TENS groups

Variable	**KI**			**TENS**		
	Pre	Post	*p*	Pre	Post	*p*
Pain (VAS)	7.9±1.0	1.6±1.0	<0.001	7.7±1.2	1.8±1.0	<0.001
ROM (degrees	105.6±8.6	130.3±5.8	<0.001	103.0±6.6	126.1±8.6	<0.001

Key: KI = ketoprofen Iontophoresis group; TENS = Transcutaneous Electrical Nerve Stimulation group; VAS = Visual Analog Scale; ROM = Range of Motion

However, there was no statistically significant difference in pain intensities and ROM values comparing both the KI and TENS groups ($t = 1.11$ at $p < 0.2$ and $t = 0.44$, $p < 0.2$), which indicates that both modalities are not statistically superior to each other in relieving pain and increasing ROM in an osteoarthritic knee.

Discussion

Pain is a major symptom of OA and its effective management remains one of the most important and pressing issues of society in general (Bonica et al., 1990). The reduction in pain level and subsequent increase in ROM observed in this study in the KI group was probably due to the depth of penetration of ketoprofen into the tissue following iontophoresis. Investigators have examined the tissue permeation of NSAIDs and steroids following both topical administration (McNeil, Potts, and Francoeur, 1992; Singh and Roberts, 1994) and iontophoresis (Glass et al., 1980; Sanderson et al., 1989; and Insel, 1996). Dexamethasone phosphate iontophoresed from the anode (i.e., positive electrode) has been shown to penetrate to deep peri-articular structures in several different joints in a single monkey experiment. The presence of dexamethasone in these tissues was the result of local tissue permeation and not an effect of drug delivery by systemic circulation, the researchers argued (Glass et al., 1980). Our study findings support those two studies as the pain relief may be partially due to the ketoprofen permeation following iontophoresis and subsequent focal circulatory distribution of ketoprofen into deeper structures of the joint as suggested by Panus, Ferslew, and Tober-Meyer,(1999), and Singh and Roberts (1993).

In contrast, cathodic iontophoresis resulted in more ketoprofen in the superficial muscles. Those detected in deep muscle layers were thought to be as a result of iontophoretic transport from the superficial muscle layer, focal circulatory distribution, or other yet unexamined experimental variables (Panus, Ferslew, and Tober-Meyer, 1999). However, Singh and Roberts (1993) reported that cathodic iontophoresis of salicylic acid resulted in local transcutaneous tissue permeation down to superficial muscle, while salicylate was

said to reach deeper tissue structures below the application site only through the systemic blood stream.

Our findings contradict the study of Glass and colleagues (1980) on dexamethasone iontophoresis, but the differences are probably due to methodological variances. Glass and colleagues used a current density of 0.94mA/cm^2, while Panus, Ferslew, and Tober-Meyer (1999), Singh and Roberts (1993), and we used 0.28mA/cm^2, 0.38mA/cm^2 and 0.28mA/cm^2, respectively. It is possible that the depth of drug tissue permeation may be positively correlated to the current density. Similarly, the concentration of total ketoprofen delivered following cathodic iontophoresis in humans appeared to be directly proportional to the current density (Panus, Ferslew, and Tober-Meyer, 1996). Regardless of the exact tissue permeation depth of NSAIDs following iontophoretic application, investigators have documented local anti-inflammatory effects when NSAIDs were applied transcutaneously (Matucci-cerinic and Casini, 1988; Baixauli, Ingles, and Alcantara, 1990; Banga and Panus, 1998). Also, Radermacher, Jentsch, and Scholl (1991) documented that transcutaneously applied NSAIDs reached non-vascular compartments such as the synovium after systemic absorption from the application site and vascular distribution to the joints.

This present study is thus in line with that of Radermacher, Jentsch, and Scholl (1991) since the presence of ketoprofen in the synovium coupled with documented anti-inflammatory effects seen following iontophoresis (Baixauli et al., 1990; Banga and Panus, 1998) may be responsible for the alleviation of osteoarthritic knee pain and subsequent increase in ROM observed in this study.

Conclusion

Our findings in this pilot study showed statistically significant reduction in pain intensities and increase in ROM using either KI coupled with QSEs or TENS coupled with QSEs. However, no modality was statistically superior to the other in terms of effectiveness in the management of osteoarthritic knee pain.

Conflict of interest: *None declared.*

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