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LITERATURE REVIEW

Safety and efficacy of topical ketoprofen in transfersome gel in knee osteoarthritis: A systematic review

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Abstract

Purpose Topical ketoprofen in Transfersome gel has been used for the alleviation of symptoms in osteoarthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with various side effects. Topical NSAIDs are known to have a lower side-effect profile when compared with systemic administration. The present systematic review aimed to determine the safety and efficacy of topical ketoprofen in Transfersome gel in knee osteoarthritis (OA).

Methods A systematic literature review was performed. The electronic databases EMBASE, MEDLINE, HealthStar and PubMed were searched from 1946 to June 2016. A screen of the reference sections of the included studies was also performed. Two blinded reviewers searched, screened, abstracted and evaluated the data quality using the Jadad scale. Studies were included if they contained: at least 50% of participants with knee OA, topical ketoprofen, human subjects and participants from North America or Europe. Study outcomes had to include patient-reported functional outcome scores.

Results Five studies were included, with a total of 3619 participants, and a mean Jadad score of 3.4/5. Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index was the only outcome measure consistent across all of the randomized controlled trials included in the present review (four of the five included studies). All topical ketoprofen in Transfersome gel groups (25 mg, 50 mg and 100 mg) had improvements in pain that were superior to all other treatment arms, and the 50 mg topical ketoprofen in Transfersome gel group had functional gains that were superior to all other treatment arms. The majority of the adverse events were non-serious and related to skin and subcutaneous tissue disorders, with erythema being the most common. The average of all adverse events and gastrointestinal (GI) adverse events was highest in the oral celecoxib group (47.1% and 15.1%, respectively). The average frequency of GI adverse events in the topical ketoprofen groups was comparable with that in the topical placebo treatment arm. A meta-analysis was not feasible due to the heterogeneity among the studies.

Conclusions Topical ketoprofen in Transfersome gel is an effective means of treating symptoms of knee OA, and is superior to oral celecoxib, oral placebo and topical placebo. The most commonly reported adverse events associated with the use of topical ketoprofen in Transfersome gel were non-severe skin and subcutaneous tissue disorders. Furthermore, as topical ketoprofen in Transfersome gel was associated with fewer adverse events when compared with oral celecoxib, and had rates of GI adverse events comparable with those of topical placebo, it may be ideal for those who are unable to take oral NSAIDs.

KEYWORDS

ketoprofen, knee, osteoarthritis, topical NSAID

1 | INTRODUCTION

Osteoarthritis (OA) is a chronic condition that leads to significant pain, functional limitations and impaired quality of life owing to inflammation of the synovium and degeneration of the articular cartilage (Bijlsma, Berenbaum, & Lafeber, 2011). OA, particularly of the knee, is a commonly reported condition and its prevalence increases with age (Bijlsma et al., 2011). Therefore, with an ageing population that is continually growing, knee OA is a burden not only on individual patients, but also on healthcare (Le, Montejano, Cao, Zhao, & Ang, 2012). As there is no cure for OA, the current goals of treatment are to alleviate pain and stiffness, and maintain physical function (McAlindon et al., 2014).

Oral non-steroidal anti-inflammatory drugs (NSAIDs) and total knee replacements (TKRs) are commonly used and recommended in the treatment of knee OA (Duchman, Gao, Pugely, Martin, & Callaghan, 2014; Kingsbury, Hensor, Walsh, Hochberg, & Conaghan, 2013; Hochberg et al., 2012; Nelson, Allen, Golightly, Goode, & Jordan, 2014). Orally administered NSAIDs are associated with serious systemic adverse events (AEs), however, particularly affecting the gastrointestinal (GI) and cardiovascular (CV) systems (Bateman & Kennedy, 1995; Conaghan, 2012). TKRs are commonly reserved for end-stage knee OA (Bourne, Chesworth, Davis, Mahomed, & Charron, 2010) and are associated with various surgical risks (Duchman et al., 2014), and patients may still complain of pain after their surgery (Bourne, Chesworth, Davis, Mahomed, & Charron, 2010). The risks associated with oral NSAIDs and TKRs can be mitigated with the use of topical NSAID formulations because they have been associated with fewer systemic AEs (Heyneman, Lawless-Liday, & Wall, 2000) and are not associated with surgical risks or complications. Further, topical NSAIDs have demonstrated comparable effectiveness when compared with oral NSAIDs (Tugwell, Wells, & Shainhouse, 2004; Underwood et al., 2008). Nevertheless, there are many formulations of topical NSAIDs that may vary with regard to their pharmacological properties as well as their overall safety and efficacy (Haroutiunian, Drennan, & Lipman, 2010).

Ketoprofen is an established NSAID that has been effective in the treatment of a variety of acute and chronic pain conditions (Sarzi-Puttini et al., 2010). A topical formulation consisting of ketoprofen in the carrier Transfersome (Diractin or IDEA-033) differs from conventional topical NSAIDs (Cevc, Mazgareanu, & Rother, 2008). Owing to the properties of its carrier, a higher concentration of the medication is delivered to target tissues more directly (Cevc et al., 2008).

The aim of the present systematic review was to provide patients and clinicians with evidence-based information about the safety and efficacy of topical ketoprofen in Transfersome gel in knee OA.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Two blinded reviewers independently searched the online databases EMBASE, MEDLINE, HealthStar and PubMed from 1946 to 24 June 2016, for literature addressing topical ketoprofen (in Transfersome gel) for pain relief in knee OA. The research question and the inclusion and exclusion criteria were decided on a priori. The key terms "ketoprofen", "osteoarthritis", "knee" and "knee osteoarthritis" were used.

Duplicate screening was carried out for the titles, abstracts and full texts. Discussion between two reviewers took place to address disagreements and, if needed, the senior author resolved issues related to study selection. Studies were included if they included: (a) knee OA; (b) topical ketoprofen; (c) human subjects (i.e. no cadaveric studies); (d) participants from Europe or North America; and (e) full text. The exclusion criteria included: (a) studies reporting no topical NSAIDs; (b) studies without at least 50% of participants with knee OA; (c) conference proceedings or abstracts; and (d) literature reviews.

The Jadad scale was used to perform a quality assessment of the included studies. The Jadad scale is a three-item, validated and reliable scoring tool for randomized controlled trials (RCTs) (Olivo et al., 2008). The scale focuses on randomization, blinding and withdrawals/dropouts (Jadad et al., 1996; Olivo et al., 2008). Studies evaluated can be given a total score of 0 to 5, with 5 being the most ideal score and a score of 3 or greater considered as high quality (Chung, Dong, Jung, Wook, & Assessing the quality of randomized controlled trials published in the Journal of Korean Medical Science from 1986 to 2011, 2012).

2.2 | Data abstraction

The two reviewers abstracted the data in duplicate and kept the records in a Microsoft Excel 2007 spreadsheet. The data included year of publication, author, location of study, study design, patient demographics, type and dosage of treatment, and follow-up intervals. The outcome data were baseline and follow-up measurements of the Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index, the Patient Global Assessment, the German version of European Quality of Life (EUROQoL), the Numeric Pain Rating Scale and the Outcome Measures in Rheumatology (OMERACT) – Osteoarthritis Research Society International (OARSI) responder rates.

2.3 | Statistical analysis

An intra-class correlation coefficient (ICC) was used to determine the quality assessment score agreement (McGinn et al., 2004). For all phases of the abstract and full text screening, a weighted κ (kappa) was calculated to assess inter-rater agreement (McGinn et al., 2004). The following κ values were selected a priori: $\kappa > 0.61$ to signify substantial agreement; $0.21 < \kappa < 0.60$, to signify moderate agreement; and $\kappa < 0.20$, to signify slight agreement (McGinn et al., 2004). Descriptive statistics were reported for the studies included in the review.

3 | RESULTS

Initially, 1393 studies were found, with 12 proceeding to full-text screening, of which three were excluded for being literature reviews (Coaccioli, 2011; Herndon, 2012; Sarzi-Puttini et al., 2010), two for being abstracts or conference proceedings (Conaghan et al., 2012;

Rother, Yeoman, & Ekman, 2012), one for not being conducted in North America or Europe (Waikakul, Penkitti, Soparat, & Boonsanong, 1997) and one for being an animal study (Komatsu & Sakurada, 2012). Ultimately, five studies met the inclusion/exclusion criteria and were included in the present review (Conaghan, Dickson, Bolten, Cevc, & Rother, 2013; Kneer, Rother, Rother, & Seidel, 2009, Kneer, Rother, Mazgareanu, & Seidel, 2013; Rother et al., 2007, 2012) (Figure 1). After screening the reference sections of these studies, it did not appear as though any additional studies had been missed in the initial search.

With ICC = 0.95 (95% confidence interval = 0.88 to 0.96), high agreement was demonstrated among the quality assessment scores given to the included studies, using the Jadad scale. The included studies had a mean Jadad score of 3.4 out of 5, with scores ranging from 1 to 5 (Table 1). At both the abstract and full-text stages, reviewers had considerable agreement when selecting which articles to include, with $\kappa = 0.99$ (two out of 1040 articles in disagreement) and $\kappa = 1$, respectively. The senior author was not required to resolve inconsistencies.

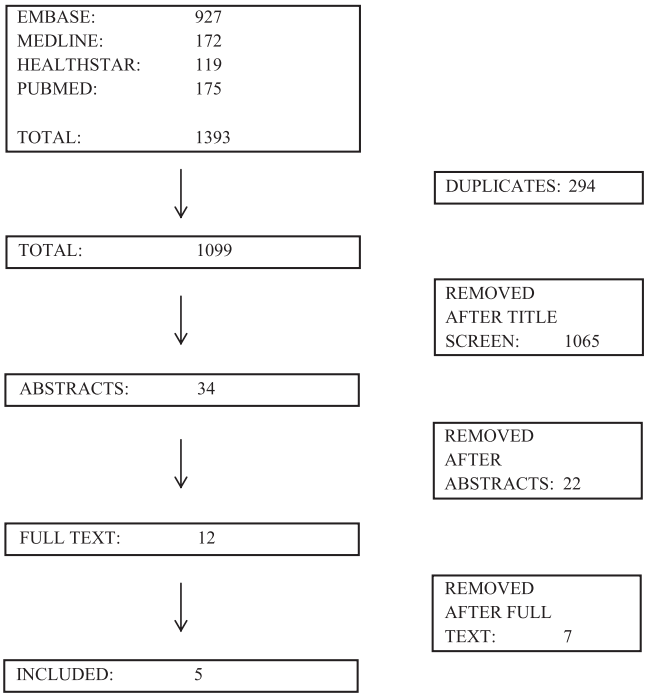

FIGURE 1 Outline of search strategy

A meta-analysis was not feasible as the study designs, comparator groups (applicable in four of the five studies), treatment dosages and patient-reported outcome measures were not consistent across all studies. Four of the five included studies were RCTs (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2013), while one of the included studies was a prospective cohort study (Kneer et al., 2009) (Table 2). All studies were conducted in Europe, and sample sizes ranged between 397 and 1399 participants (Table 3). All of the studies combined evaluated a total of 3619 participants.

In four of the five included studies (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2012), 100% of participants had a clinical diagnosis of knee OA, whereas, in one of the included studies (Kneer et al., 2009), 68.9% of participants had a diagnosis of knee OA. The latest follow-up period for the included studies ranged between six weeks and 18 months, with three of the included studies having 12 weeks as the latest follow-up period (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2013). Within the RCTs (four of the five included studies) (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2013), study completion ranged between 81.1% and 89.8%. With regard to the non-randomized study, 54% of participants documented more than 80% of their treatment applications (Kneer et al., 2009). All five studies had an intent–to-treat population. All of the studies had topical ketoprofen in Transfersome gel as the intervention, with dosages ranging from 25 mg to 110 mg (applied twice daily) across studies. All of the RCTs used TDT 064 as the vehicle for the ketoprofen-free topical placebo (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2013). Other comparator treatment arms included were oral celecoxib and/or oral placebo (Conaghan et al., 2013; Rother et al., 2007). All RCTs had comparable baseline characteristics across treatment arms.

A variety of outcome measures were utilized across the included studies. All studies found improvements with the use of topical ketoprofen in Transfersome gel for the treatment of symptoms of knee OA. WOMAC was the only outcome measure consistent across all of the RCTs included in the review (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2013). When comparing topical ketoprofen with placebo (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2013), two of the four studies found better improvements in the topical ketoprofen in Transfersome gel

TABLE 1 Jadad scale

	Potential score	Kneer et al. (2013)	Rother et al. (2007)	Conaghan et al. (2013)	Rother et al. (2013)	Kneer et al. (2009)
Was the study described as randomized?	+1	1	1	1	1	0
Was the method of randomization described and appropriate?	+1	0	1	1	1	0
If described and inappropriate, describe:	−1	0	0	0	0	0
Was the study described as double-blinded?	+1	1	1	1	1	0
Was the method of double-blinding described and appropriate to maintain a double-blinding?	+1	0	0	1	0	0
Was the method of blinding inappropriate?	−1	0	0	0	0	0
Was there a description of withdrawals and drop outs?	+1	1	1	1	1	1
TOTAL SCORE /5	5	3	4	5	4	1

TABLE 2 Results of included studies

	Kneer et al. (2013)	Rother et al. (2007)	Conaghan et al. (2013)	Rother et al. (2013)	Kneer et al. (2009)	Average
T	RCT	RCT	RCT	RCT	PC	NA
L	I	I	I	I	III	NA
Year	2013	2007	2013	2013	2009	NA
SS-K-100	211	138	230	274	NA	853
SS-K-50	213	NA	233	NA	NA	446
SS-K-25	214	NA	NA	NA	NA	214
SS-TDT	190	127	234	281	NA	832
SS-OC	NA	132	233	NA	NA	365
SS-OP	NA	NA	227	NA	NA	227
WP-K-100	57.4	35.2	40.9	38.1	NA	43.1
WP-K-50	57.1	NA	40.8	NA	NA	48.6
WP-K-25	53.4	NA	NA	NA	NA	53.4
WP-TDT	49.5	20.7	37.82	44.0	NA	40.0
WP-OC	NA	36.9	40.43	NA	NA	39.2
WP-OP	NA	20.7	29.3	NA	NA	26.2
WF-K-100	42.0	32.4	NA	37.4	NA	37.9
WF-K-50	44.7	NA	NA	NA	NA	44.7
WF-K-25	37.1	NA	NA	NA	NA	37.1
WF-TDT	36.1	23.2	NA	43.0	NA	40.2
WF-OC	NA	35.8	NA	NA	NA	35.8
WF-OP	NA	23.2	NA	NA	NA	23.2
AE-K-100	50.7	53.6	44.4	24.5	NA	41.1
AE-K-50	51.6	NA	39.5	NA	NA	45.3
AE-K-25	47.1	NA	NA	NA	NA	47.1
AE-TDT	46.7	48.8	45.1	23.5	NA	38.7
AE-OC	NA	50.0	45.5	NA	NA	47.1
AE-OP	NA	NA	45.8	NA	NA	45.8
AGE-K-100	4.5	9.4	1.3	0.4	NA	3.1
AGE-K-50	2.7	NA	1.3	NA	NA	2.0
AGE-K-25	2.7	NA	NA	NA	NA	2.7
AGE-TDT	4.5	9.4	1.9	0.4	NA	3.1
AGE-OC	NA	13.6	15.9	NA	NA	15.1
AGE-OP	NA	NA	14.5	NA	NA	14.5

AE-K-25, adverse events ketoprofen in Transfersome gel (25 mg); AE-K-50, adverse events ketoprofen in Transfersome gel (50 mg); AE-K-100, adverse events ketoprofen in Transfersome gel (100 mg); AE-OC, adverse events oral celecoxib; AE-OP, adverse events oral placebo; AE-TDT, adverse events Transfersome gel without ketoprofen; AGE-K-25, adverse gastrointestinal events ketoprofen in Transfersome gel (25 mg); AGE-K-50, adverse gastrointestinal events ketoprofen in Transfersome gel (50 mg); AGE-K-100, adverse gastrointestinal events ketoprofen in Transfersome gel (100 mg); AGE-OC, adverse gastrointestinal events oral celecoxib; AGE-OP, adverse gastrointestinal events oral placebo; AGE-TDT, adverse gastrointestinal events Transfersome gel without ketoprofen; NA, not applicable; L, level; PC, prospective cohort; RCT, randomized controlled trial; SS-K-25, sample size ketoprofen in Transfersome gel (25 mg); SS-K-50, sample size ketoprofen in Transfersome gel (50 mg); SS-K-100, sample size ketoprofen in Transfersome gel (100 mg); SS-OC, sample size oral celecoxib; SS-OP, sample size oral placebo; SS-TDT, sample size Transfersome gel without ketoprofen; T, type of study; WF-K-25, WOMAC function scale ketoprofen in Transfersome gel (25 mg); WF-K-50, WOMAC function scale ketoprofen in Transfersome gel (50 mg); WF-K-100, WOMAC function scale ketoprofen in Transfersome gel (100 mg); WF-OC, WOMAC function scale oral celecoxib; WF-OP, WOMAC function scale oral placebo; WF-TDT, WOMAC function scale Transfersome gel without ketoprofen; WOMAC, Western Ontario McMaster Universities; WP-K-25, WOMAC pain scale ketoprofen in Transfersome gel (25 mg); WP-K-50, WOMAC pain scale ketoprofen in Transfersome gel (50 mg); WP-K-100, WOMAC pain scale ketoprofen in Transfersome gel (100 mg); WP-OC, WOMAC pain scale oral celecoxib; WP-OP, WOMAC pain scale oral placebo; WP-TDT, WOMAC pain scale Transfersome gel without ketoprofen.

group (Kneer et al., 2013; Rother et al., 2007), one of the four studies found no difference between the topical ketoprofen and topical placebo groups (Conaghan et al., 2013) and one of the four studies concluded that placebo had better results (Rother et al., 2013). Nevertheless, after combining the results of these studies, each dosage of ketoprofen in Transfersome gel was found to be superior to topical placebo (TDT 064), oral placebo and oral celecoxib with regard to pain. With regard to functional improvements, 50 mg ketoprofen in Transfersome gel was superior to all other treatment arms. For the topical ketoprofen in Transfersome gel groups, the ketoprofen dosages of 100 mg, 50 mg and 25 mg had values of −43.1%, −48.6% and −53.4%, respectively, for pain, and −37.9%, −44.7% and −37.1%, respectively, for function. For the pain and functional scales, the topical placebo (TDT 064) group had values of −40.0% and

TABLE 3 Study characteristics

	Kneer et al. (2013)	Rother et al. (2007)	Conaghan et al. (2013)	Rother et al. (2013)	Kneer et al. (2009)
Overall sample size	866	397	1399	555	402
Percentage of those with a clinical diagnosis of knee OA	100%	100%	100%	100%	68.9%
Baseline characteristics	Similar baseline characteristics	Similar baseline characteristics	Similar baseline characteristics	Similar baseline characteristics	No comparator group
Percentage of those who completed study	82.8%	81.6%	89.8%	81.1%	54% documented more than 80% of their treatment applications.
Follow-up periods	Weeks 2, 6 and 12	Weeks 2, 4 and 6	Weeks 2, 6, 9 and 12	Weeks 2, 6, 9 and 12	36-month study after 18 months of exposure
Intervention	Ketoprofen in Transfersome gel: 25 mg, 50 mg or 100 mg	Ketoprofen in Transfersome gel: 110 mg	Ketoprofen in Transfersome gel: 50 mg or 100 mg	Ketoprofen in Transfersome gel: 50 mg or 100 mg	Ketoprofen in Transfersome gel: 110 mg, with a maximum of 2 applications per day
Comparator treatment arms	Topical placebo (TDT 064)	Topical placebo (TDT 064) Oral placebo Oral celecoxib	Topical placebo (TDT 064) Oral celecoxib Oral placebo	Topical placebo (TDT 064)	No comparator group
Intent-to-treat population	Yes	Yes	Yes	Yes	Yes
Outcome measures	WOMAC Osteoarthritis Index, numeric pain rating, OMERACT–OARSI responder rates	WOMAC Osteoarthritis Index	WOMAC Osteoarthritis Index	WOMAC Osteoarthritis Index, numeric pain rating	Numeric pain rating, German version of EuroQol
Findings	Better improvements in the topical ketoprofen in Transfersome gel group	Better improvements in the topical ketoprofen in Transfersome gel group	No difference between topical placebo and topical ketoprofen	Placebo had better results	Adequate improvement with the use of topical ketoprofen in Transfersome gel

EuroQol, European Quality of Life; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OMERACT, Outcome measures in Rheumatology; WOMAC, Western Ontario and McMaster Universities.

−40.2%, respectively. The oral celecoxib group had values of −39.2% and −35.8% for pain and function, respectively. Oral placebo had values of −26.2% and −23.2% for pain and function, respectively (Table 1).

The majority of the AEs were non-serious and related to skin and subcutaneous tissue disorders, with erythema being the most common. The total weighted average frequency of all AEs was highest in the oral celecoxib group (47.1%) and the 25 mg topical ketoprofen in Transfersome gel group (47.1%), followed by the oral placebo group (45.8%), the 50 mg topical ketoprofen in Transfersome gel group (45.3%), the 100 mg topical ketoprofen in Transfersome gel group (41.1%) and the oral placebo (TDT 064) group (38.7%). When examining GI AEs, the total weighted average was highest among the oral celecoxib group (15.1%), followed by: the oral placebo group (14.5%), the TDT 064 group (3.1%), the 100 mg topical ketoprofen in Transfersome gel group (3.1%), the 25 mg topical ketoprofen in Transfersome gel group (2.7%) and the 50 mg topical ketoprofen in Transfersome gel group (2.0%) (Table 1).

4 | DISCUSSION

The present systematic review examined the safety and efficacy of topical ketoprofen in Transfersome gel in knee OA. To the authors' knowledge, this was the first systematic review conduced on this specific topic. The results of the review, with five studies included, demonstrated that: (a) topical ketoprofen in Transfersome gel appears to be an effective means of treating symptoms of knee OA; (b) topical ketoprofen in Transfersome gel appears to be more effective than oral NSAIDs and placebo for treating knee OA; (c) minor, dermal AEs, specifically erythema, are the most common AEs reported with the use of topical ketoprofen in Transfersome gel; and (d) further studies are warranted.

When examining the effects of topical ketoprofen in Transfersome gel in isolation (i.e. without using a comparator group) on patients with knee OA, positive outcomes are noted across the studies in terms of pain and function, particularly as indicated by WOMAC, a self-reported outcome measure which evaluates three dimensions of pain, stiffness and physical function with maximum scores of 20, 8 and 68, respectively. A lower score indicates a lower level of symptoms and/or physical disability (McConnell, Kolopack, & Davis, 2001). There has been little evidence of test–retest reliability for the stiffness subscale (McConnell et al., 2001). The physical function subscale has been found to be inadequate in detecting changes in the setting of a weak association between pain and function (Pua, Cowan, Wrigley, & Bennell, 2009). Nevertheless, in various studies over the last 30 years, the WOMAC score has been shown to be a sensitive, reliable and valid functional outcome measure

for hip and knee OA (McConnell et al., 2001; Williams, Piva, Irrgang, Crossley, & Fitzgerald, 2012).

Positive outcomes have consistently been reported in the literature, when examining the efficacy of topical ketoprofen (different types) in the treatment of various acute and chronic conditions (Fulga, Lupescu, & Spircu, 2012; Mason, Moore, Edwards, Derry, & McQuay, 2004; Massey, Derry, Moore, & McQuay, 2010; Moore, Tramèr, Carroll, Wiffen, & McQuay, 1998; Rother et al., 2009).

An important indicator of an effective treatment is whether it has attained the minimal clinically important improvement (MCII), which is the smallest change that is required in an outcome measure in order to identify the improvement as significant or important to patients with regard to their symptoms (Tubach et al., 2005). The absolute and relative MCIIs for the WOMAC pain scale are −40.8% and −32.0%, respectively, for someone with knee OA (Tubach et al., 2005). The absolute and relative MCIIs for the WOMAC functional scale are −26.0% and −21.1%, respectively, for someone with knee OA (Tubach et al., 2005). When the results for the WOMAC pain and functional scales were combined across the studies, each of the topical ketoprofen groups (100 mg, 50 mg and 25 mg) satisfied the absolute and relative MCIIs for pain and function; however, this was not the case for any of the comparator groups. The topical placebo (TDT 064) and oral celecoxib groups satisfied the relative MCII for pain and the absolute MCII for function. The oral placebo group only satisfied the relative MCII for function. Although values among the treatment arms were close, topical ketoprofen in Transfersome gel, all dosages and 50 mg, had the highest values for pain and function, respectfully. Further, when placing the values of the treatment arms in the perspective of the MCII, topical ketoprofen in Transfersome gel may be considered superior to oral celecoxib, oral placebo and topical placebo (TDT 064).

A placebo effect in knee OA has been documented in the literature (Doherty & Dieppe, 2009; Zhang, Robertson, Jones, Dieppe, & Doherty, 2008); therefore, the expectation of pain relief, for example, may have resulted in substantial gains in pain and function. As all the included studies with a placebo comparator group (four of the five studies) (Conaghan et al., 2013; Kneer et al., 2013; Rother et al., 2007, Rother et al., 2013) had a follow-up period of 12 weeks or less, it is questionable as to whether the gains from the placebo effect would continue over a longer duration.

All five of the included studies had a dosage of ketoprofen ranging from 25 mg to 110 mg, which is less than the daily maximum of 300 mg or the recommended dosage of 200 mg/day (Chou, McDonagh, Nakamoto, & Griffin, 2011).

The results of the present systematic review demonstrated that although AEs occur with the use of topical ketoprofen in Transfersome gel, they are most commonly associated with non-serious dermal reactions, such as erythema. Although the topical ketoprofen in Transfersome gel and oral NSAID (celecoxib) groups have demonstrated effective results, the topical ketoprofen groups had fewer AEs, particularly related to the GI system, with average GI AEs comparable with those of oral placebo (TDT 064). Therefore, individuals who are unable to take oral NSAIDs because of contraindications or the fact that they are taking concomitant medications might benefit from applying topical ketoprofen in Transfersome gel. A systematic review from 2010 also demonstrated that topical NSAIDs are safer than oral NSAIDs when examining GI AEs; however, mild systemic AEs have been reported for older adults using topical NSAIDs to treat OA (Makris, Kohler, & Fraenkel, 2010). Overall, topical NSAID manufacturers list history of asthma, urticaria, cardiovascular disease and GI bleeding as contraindications to their use (Cheng & Visco, 2012). Clinicians should be cautious about the above-mentioned manufacturer suggestions during clinical applications of topical ketoprofen for knee OA.

The present systematic review had various limitations and demonstrated that further high-quality studies are warranted. Only five studies met the inclusion/exclusion criteria and one was not a RCT. Not all of the studies had comparable outcome measures, which would have been optimal for more comprehensive comparisons across studies. Not all of the RCTs contained the same treatment arms, so there were fewer values when averaging the overall results for some of the treatment arms. The longest follow-up within the RCTs was 12 weeks, which would not have provided enough information about the long-term effects of topical ketoprofen in Transfersome gel.

A strength of the present systematic review was the studies it incorporated, with four of five studies considered to be of high quality, based on the Jadad scale. All RCTs had an acceptable completion rate of greater than 80% and all studies utilized an intent-to-treat population. Four of the five studies were RCTs, which is the most ideal design for treatment studies, and each of these had treatment arms of participants with comparable baseline characteristics.

5 | CONCLUSION

The current evidence examined in the present review supports the trend of topical ketoprofen in Transfersome gel as an effective means of treating patients with knee OA, with overall improvements in pain and function, superior to oral celecoxib, oral placebo and topical placebo. The most commonly reported AEs associated with the use of topical ketoprofen in Transfersome gel were non-severe skin and subcutaneous tissue disorders, such as erythema. Furthermore, as topical ketoprofen in Transfersome gel was associated with fewer AEs when compared with oral celecoxib, and had rates of GI AEs comparable with topical placebo, it may be ideal for those who are unable to take oral NSAIDs.

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