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Review article

A systematic review and meta-analysis of oxaceprol in the management of osteoarthritis: An evidence from randomized parallel-group controlled trials

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ABSTRACT

Oxaceprol, a derivative of L-proline, is an established drug for managing osteoarthritis (OA) with better safety profile than non-steroidal anti-inflammatory drugs (NSAIDs). This systematic review and meta-analysis, following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, evaluated the efficacy, safety and tolerability of oxaceprol in OA. Electronic databases for published and grey (unpublished) literature were searched to identify parallel-group randomized controlled trials (RCTs) evaluating the impact of oxaceprol in patients with OA. Risk of bias was assessed using the Cochrane collaboration's tool. A total of seven parallel-group RCTs involving 1087 participants were included in the systematic review. Meta-analysis, in Review Manager, demonstrated numerically greater/significant improvements compared to active control [diclofenac/ibuprofen]/placebo in pain and function of joint; similar improvement *vs.* active control in global treatment efficacy; no difference/significant difference *vs.* active control/placebo in NSAIDs as rescue medication. Treatment with oxaceprol showed numerically less adverse events (AEs) than active control (diclofenac: risk ratio [RR], 0.71; 95% confidence interval [CI], 0.45 to 1.11; $p = 0.14$: ibuprofen: RR, 0.73; 95% CI, 0.30 to 1.78; $p = 0.49$) and significantly fewer AEs compared to placebo (RR, 0.76; 95% CI, 0.63 to 0.92; $p = 0.004$). Given the nature of small-to-moderate sample size and short duration of eligible studies, the available clinical evidence of oxaceprol in the management of OA is modest – though looks promising. New and better RCTs with larger sample size and longer follow-up are warranted to strengthen the use of oxaceprol in clinical setting for managing OA.

Contents

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Introduction

Osteoarthritis (OA), a chronic and progressive degenerative joint disease or degenerative arthritis, is the most common chronic condition of the joints, affecting most often the knees, hips, and hands [1,2]. The prevalence and incidence of OA vary depending on: non-modifiable systematic risk factors, such as age, sex, genetics, and ethnicity; modifiable systematic risk factors including obesity, diet, and bone metabolism; modifiable local risk factors like muscle strength, physical activity/occupation, joint injury, joint alignment, and leg length inequality [3]. The latest World Health Organization (WHO) data report OA as one of the ten most disabling diseases in developed countries. Globally, about 9.6% and 18% of men and women, respectively, aged older than 60 years are diagnosed with symptomatic OA. Around 25% of the OA population is unable to perform their major daily activities of life, and 80% have restricted movements [1], resulting in increased risk for all-cause mortality [4]. It is estimated that, by 2050, worldwide no less than 130 million people will be impacted from OA [5].

Management of OA is primarily categorized as: non-pharmacologic, pharmacologic, complementary and alternative, and surgical [6]. Currently, the management of OA is merely palliative and principally focused on the alleviation of pain and symptoms [7]. In general, non-pharmacologic management recommends diet and encourages regular exercise to lose weight in case of obesity or overweight; one of the most important modifiable systematic risk factors [3,6,7]. Complementary and alternative approach is widely recommended which involves acupuncture, heat and cold pad, balneotherapy, orthosis, glucosamine, chondroitin, capsaicin cream, S-adenosylmethionine; however, clinical practice data show limited use of several of these in managing OA [6–8]. The surgical interventions are arthroscopy, joint lavage, and total joint replacement; these options are reserved for those who do not show any improvement with non-pharmacologic, complementary and alternative, as well pharmacologic approach [6,7]. Pharmacologically, non-steroidal anti-inflammatory drugs (NSAIDs) are the cornerstone in the management of OA pain [9,10]. The drug utilization studies, in different parts of the world, reported that NSAIDs are most widely prescribed in managing OA pain [11–15]. The recent study by da Costa and team assessed the efficacy of NSAIDs for treating knee and hip OA pain and reported that paracetamol is clinically ineffective to be recommended for the symptomatic management of OA, irrespective of dose. Further, the study noted sound evidence on diclofenac (150 mg/day) use for improving pain and physical function [10]. However, the accumulated clinical evidence generally recommends to consider the gastrointestinal (GI), cardiovascular (CV), and other safety profile of NSAIDs before prescribing for OA patient population [16–24].

Oxaceprol (Anatomical Therapeutic Chemical [ATC] code: M01AX24), a derivative of L-proline with distinct anti-inflammatory activity, has been widely used in managing OA since several years [25]; Table S1 lists various proprietary (trade) products containing oxaceprol with their respective manufacturer and country. Oxaceprol mainly acts by inhibiting leukocyte adhesion and migration [25,26]; however, NSAIDs act by peripheral inhibition of prostaglandin (PG) synthesis and a variety of other peripheral and central mechanisms [27]. This unique mechanism of oxaceprol in ameliorating OA pain and stiffness demonstrates better GI safety, in particular when compared with NSAIDs [25,28–32]. A recent experimental comparative study evaluated the therapeutic efficacy of intra-articular injection of oxaceprol and corticosteroid. The study reported improvement of articular cartilage with oxaceprol treatment in monosodium iodoacetate-induced OA in experimental rabbits. Oxaceprol, after 28 days of treatment, was therapeutically equivalent to corticosteroid in reducing knee swelling and pain (analgesic activity) – measured *via* wire walking and hot plate methods. Histological assessment reported that oxaceprol supplementation protected articular cartilages from degenerative changes in OA. Further, comparable improvement in bone and cellular matrixes was observed with oxaceprol and corticosteroid treatment [33].

Building on the above facts, the present study aimed to systematically assess the clinical efficacy, safety and tolerability of oxaceprol in the management of OA. The authors, in addition, sought to draw a conclusion whether oxaceprol finds its place in managing OA.

Methods

Literature search

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [34]. Electronic literature search from the earliest available date to December 2017 was performed in PubMed/MEDLINE, Scopus, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases using the MeSH terms/Emtree (for EMBASE)/keywords related to oxaceprol and OA: “N-acetyl-4-hydroxyproline” OR “N-acetylhydroxyproline” OR “N-acetyl cis-4-hydroxy-L-proline” OR “oxaceprol” AND “osteoarthritis” OR “osteoarthritis, knee” OR “osteoarthritides, knee” OR “gonarthrosis” OR “osteoarthritis, hip” OR “osteoarthritides, hip” OR “coxarthrosis.” Grey (unpublished) literature was searched in the following trial registries: US National Institutes of Health (NIH; https://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (ICTRP; http://apps.who.int/trialsearch/). The US Food and Drug Administration (USFDA) website (https://www.fda.gov/) was also searched for additional documents, if any. The search was not restricted to any publication language or status of the trial. Furthermore, the reference lists of all relevant articles were hand-searched to find additional studies.

Inclusion and exclusion criteria

Studies with the following criteria were included: (i) adults of either sex with OA; (ii) oxaceprol (monotherapy or in combination with other treatments) as intervention *vs.* placebo or active treatments; (iii) parallel-group randomized controlled trials (RCTs); (iv) report at least one of the following outcomes: pain and function of joint, Quality of Life (QoL), efficacy judgment by investigators/physicians and patients, and safety and tolerability. Studies with the following criteria were excluded: (i) cross-over RCT, observational and uncontrolled studies, reviews, letters, and animal studies; (ii) commentaries and conference proceedings; (iii) duplicate studies.

Data extraction and quality (risk of bias) assessment

Potentially relevant article titles and abstracts were screened based on the inclusion criteria. Whenever required, full-text articles were retrieved. Two authors were independently involved in all stages of study selection and data extraction. Risk of bias of the eligible RCTs was assessed using the Cochrane collaboration's tool [35]. Disagreements between reviewers, if any, were resolved by discussion to obtain a consensus.

Statistical analysis

Outcomes were pooled using mean differences (MDs: inverse variance [IV] method) and Mantel-Haenszel risk ratios (RRs) with 95% confidence intervals (CIs). Heterogeneity was assessed by calculating the I^2 statistic (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity) [36]. However, the interpretation of I^2 can be misleading, as the importance of inconsistency depends on numerous factors. Considering this: as the overall population from included trials had either knee and/or hip OA; different doses of oxaceprol (200 or 400 mg bid) and diclofenac (25 or 50 mg bid); varying trial duration (20–152 days) of the selected studies; majority of OA patients, in addition to oxaceprol or active treatment, were on daily physiotherapy. In view of these factors, a random-effects model was used in all outcomes to address the variation across studies [37]. We used Adobe® Reader® XI inbuilt measuring tool, version 11.0.23 (Adobe Systems Incorporated, San Jose, California, USA), to extract the numerical values from graphs – if the study reported result(s) only in graphical form. Meta-analysis was performed using the Review Manager (RevMan; Computer program), version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Individual outcomes were represented graphically using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA, USA. In all the analyses, p value < 0.05 (two-tailed test) was considered statistically significant.

Results

Study selection and characteristics of included studies

Fig. 1, the PRISMA flow-chart, depicts the work-flow of study selection process. A total of seven RCTs (comprising 1087 patients with OA of the knee and/or hip) met the inclusion criteria [28–30,32,38–40]. Hand-searching the references of included articles resulted in an additional RCT which met the inclusion criteria [32]. Six RCTs assessed the effect of oxaceprol (200 mg or 400 mg tid) *vs.* placebo [38,40] or active treatments; diclofenac (25 mg or 50 mg tid) [28,29], and ibuprofen (400 mg tid) [30,32]. However, except Feldman et al. [38], in all the five included trials – the patients

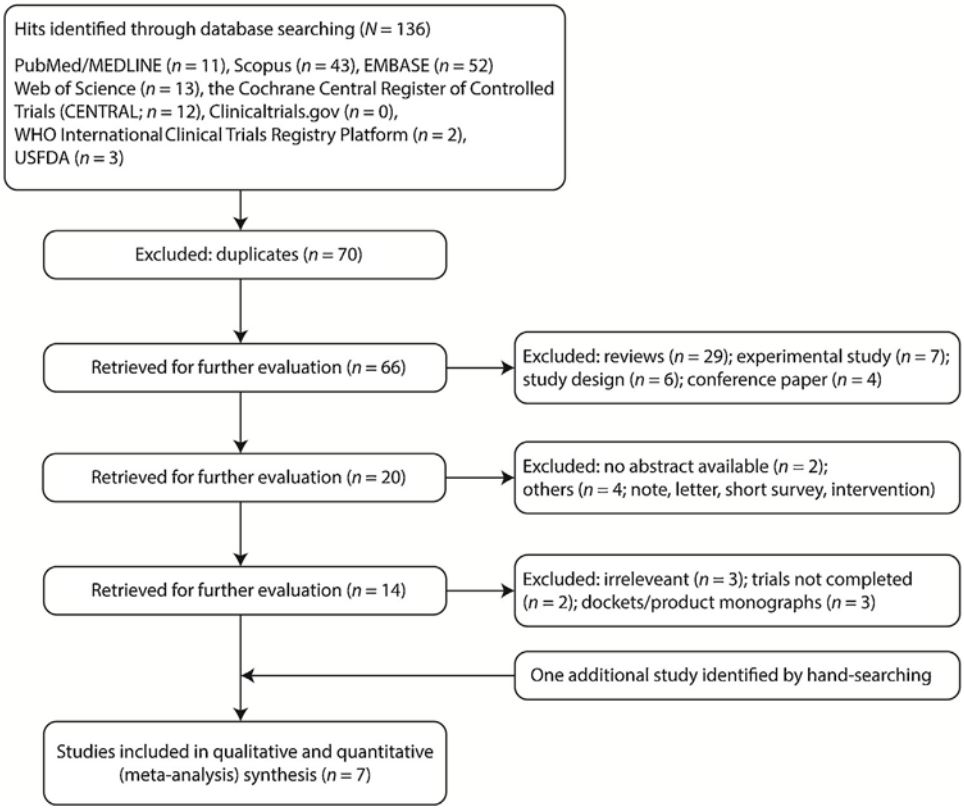

Fig. 1. PRISMA flow-chart.

received daily physiotherapy in addition to oxaceprol or active treatments/placebo. In another study, patients, besides oxaceprol, received conventional treatment (CT) and were compared to CT alone [39]: CT could include analgesics, NSAIDs, local infiltrations of corticosteroids and non-medicinal treatments such as kinesitherapy. The duration of included studies ranged between 20–152 days. The characteristics of the seven RCTs are summarized in Table 1. Further, we found two potentially relevant RCTs (CTRI/2009/091/000798 and CTRI/2014/08/004821), not yet completed or still recruiting participants [41,42]; Table 2 summarizes the available data for these two RCTs.

Quality (risk of bias) assessment

The overall quality assessment of eligible trials showed low risk of bias in the six items of the Cochrane collaboration's tool (Fig. 2a and b). However, the study by Juvin [39] showed high-risk for performance and detection bias, as the trial design masking was open-label (no blinding of patients, providers or outcome assessors). In addition, some studies did not report the following details: methods for generating the random sequence [29,30,38] and allocation concealment [28,30,38,39]. The authors' support for risk of bias judgment is detailed in Supplementary material (Table S2).

Pain and function of joint

Lequesne joint function index

Oxaceprol, compared to diclofenac, showed numerically better improvement in the Lequesne joint function index (MD, –0.29; 95% CI, –1.13 to 0.54; $p = 0.49$). However, oxaceprol in combination with CT showed significant improvement (MD, –2.20; 95% CI, –2.93 to –1.47; $p < 0.00001$) *vs.* CT alone, Fig. 3. Krüger et al. also concluded better improvement with oxaceprol supplementation than placebo (2.4 points *vs.* 1.5 points) with no statistical significance [40].

Joint mobility

Treatment with oxaceprol, compared to diclofenac and ibuprofen, exhibited similar improvement in joint mobility with no significant differences [28–30,32]. Further, oxaceprol compared to placebo, also showed clinical improvement in joint mobility [38,40].

Pain at rest and weight-bearing pain

The meta-analysis findings showed that oxaceprol is as effective as diclofenac in improving pain at rest (MD, 0.05; 95% CI, –0.42 to 0.53; $p = 0.83$) and weight-bearing pain (MD, 0.02; 95% CI, –0.52 to 0.56; $p = 0.94$), Fig. 4a and b, respectively. Oxaceprol and ibuprofen produced significant reduction (percentage change from baseline) in pain at rest (also start-up pain) with numerically improved

Table 1
Characteristics of included trials.

Author(s)/ Country	Study Design	Sample size (*N*) (Gender; M/F: Age; mean ± SD/range)	Treatments Duration	Outcomes
Bauer 1999 [28]/ Germany	Randomized, double-blind, controlled multi-center phase IV trial	*N* = 124 Oxaceprol (*n* = 34/28; 56.5 ± 10.1) Diclofenac (*n* = 34/28; 57.5 ± 10.8)	Oxaceprol, 200 mg tid Diclofenac, 25 mg tid 20 days	*Primary*: Lequesne joint function index, joint mobility *Secondary*: pain at rest, weight-bearing pain, pain-free walking time, global treatment efficacy, rescue medication (paracetamol up to 3000 mg/day), adverse effects
Feldman 1994[a] [38]/ France	Randomized, double-blind, placebo-controlled multi-center trial	*N* = 21 Oxaceprol (*n* = 10) Placebo (*n* = 11)	Oxaceprol, 200 mg tid Placebo 8 weeks	*Primary/Secondary*: joint mobility, functional capacity, pain intensity, adverse effects
Herrmann 2000 [29]/ Germany	Randomized, double-blind, controlled multi-center phase IV trial	*N* = 219 Oxaceprol (*n* = 42/68; 63.0 ± 13.3) Diclofenac (*n* = 50/59; 60.5 ± 12.2)	Oxaceprol, 400 mg tid Diclofenac, 50 mg tid 21 days	*Primary*: Lequesne joint function index, joint mobility *Secondary*: pain at rest, pain on movement (active and passive), pain-free walking time, pain in weight-bearing and weight relieving positions, global treatment efficacy, rescue medication (paracetamol up to 3000 mg/day), adverse effects
Hildebrandt 1995 [30]/ Germany	Randomized, double-blind, controlled single-center phase IV trial	*N* = 64 Oxaceprol (*n* = 16/15; 54.9 ± 10.4) Ibuprofen (*n* = 15/18; 55.7 ± 7.7)	Oxaceprol, 400 mg tid Ibuprofen, 400 mg tid 24 days	*Primary/Secondary*: Lequesne joint function index, start-up pain, pain at rest, pain on movement (active and passive), pain in relief position, pain during exercise
Juvin 1998 [39]/ France	Randomized, open-label, controlled multi-center phase IV trial	*N* = 446 Oxaceprol + Conventional treatment (CT; *n* = 167/76; 67.6 ± 6.4) CT (*n* = 140/63; 67.9 ± 6.0)	Oxaceprol, 200 mg + CT, 152 days CT, 107 days	*Primary*: QoL (EMIR; Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde), NSAIDs and analgesic use *Secondary*: Lequesne's joint function index, pain score, overall assessments by the patients and by the physicians, rescue medication (NSAIDs)
Krüger 2007 [40]/ Germany	Randomized, double-blind, placebo-controlled multi-center trial	*N* = 153 (safety analysis) *N* = 97 (efficacy analysis) Oxaceprol (safety, *n* = 25/52; 59.9 ± 9.8: efficacy, n = 20/36; 59.4 ± 9.1) Placebo (safety, *n* = 28/48; 60.5 ± 9.4; efficacy, *n* = 11/30; 59.9 ± 7.8)	Oxaceprol, 400 mg tid Placebo of identical appearance 21 days	*Primary*: pain following exercise *Secondary*: pain at rest, Lequesne joint function index, global assessment of joint disability and joint complaint, global assessment of efficacy and safety of therapy, rescue medication (acetaminophen tablets 0.5 g), drop-out due to lack of efficacy, adverse effects
Vagt 1990 [32]/ Germany	Randomized, double-blind, controlled single-center trial	*N* = 60 Oxaceprol (*n* = 14/16; 59.3 ± 11.5) Ibuprofen (*n* = 14/16; 58.9 ± 12.9)	Oxaceprol, 400 mg tid, 27 days Ibuprofen, 400 mg tid, 26 days	*Primary/Secondary*: joint mobility, pain during passive and active exercise, pain free duration, resting/stress pain, change in the onset pain, rescue medication (paracetamol up to 3000 mg/day), adverse effects

Abbreviations: F, female; M, male; *n*, number of subjects in each group; *N*, total number of subjects in the trial; NSAIDs, nonsteroidal anti-inflammatory drugs; QoL, Quality of Life; SD, standard deviation; tid, three times in a day.

[a] 7 Clinical trials: six were double-blind cross-over, and the seventh was parallel-group. No details were available on gender and age.

Table 2
Characteristics of unpublished trials.

Trial ID	Study Design Target Sample Size (*N*)	Inclusion Criteria	Treatments Duration	Outcomes
CTRI/2009/091/000798 [41]	Randomized, single-blind, controlled multi-center phase III trial *N* = 200	Patients (age, >18 years) with: - history of signs and symptoms of osteoarthritis - having normal hematology, renal/liver function test - willing to give written informed consent - willing to come to OPD for follow up	Oxaceprol (capsule), 200 mg tid Diclofenac (tablet), 50 mg tid 3 weeks	*Primary*: changes in pain (VAS), stiffness, QOL questionnaires (WOMAC INDEX) *Secondary*: adverse events, rescue medication, change in the pathological parameters
CTRI/2014/08/004821 [42]	Randomized, single-blind, controlled multi-center phase IV trial *N* = 100	Patients of either sex (age, above 50 years) with: - clinically diagnosed primary symptomatic osteoarthritis affecting at least one knee joint - knee joint pain present for at least a month in the preceding three months with at least morning stiffness less than 30 min or knee crepitus - knee pain on movement of intensity at least 35 mm on a 100 mm VAS scale	Oxaceprol (capsule), 200 mg tid Tramadol (capsule), 50 mg tid 12 weeks	*Primary*: effectiveness of oxaceprol in symptomatic primary osteoarthritis of the knee *Secondary*: safety profile of oxaceprol

Abbreviations: OPD, outpatient department; QoL, Quality of Life; tid, three times in a day; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.

group difference in oxaceprol [30], Fig. S1. Vagt et al. reported significant reduction of resting/stress pain compared to initial situation during oxaceprol and ibuprofen treatments with no difference between the groups [32]. Further, compared to placebo, there was a statistically significant ($p = 0.016$) improvement in mean pain at rest in the oxaceprol group [40], Fig. S2.

Pain-free walking time/pain-free duration

Treatment with oxaceprol and diclofenac increased median pain-free walking time by more than two-fold at end of the study, Fig. S3. The pain-free duration significantly increased in OA patients treated with oxaceprol and ibuprofen – with better clinical difference in oxaceprol, Fig. S3.

Pain on movement (active and passive)

Oxaceprol *vs.* diclofenac and ibuprofen confirmed similar efficacy in reducing pain on movement (active and passive) by end of the treatment, Figs. S1 and S4. Further, the initial pain on movement was also similarly improved under both oxaceprol and diclofenac treatments, Fig. S4.

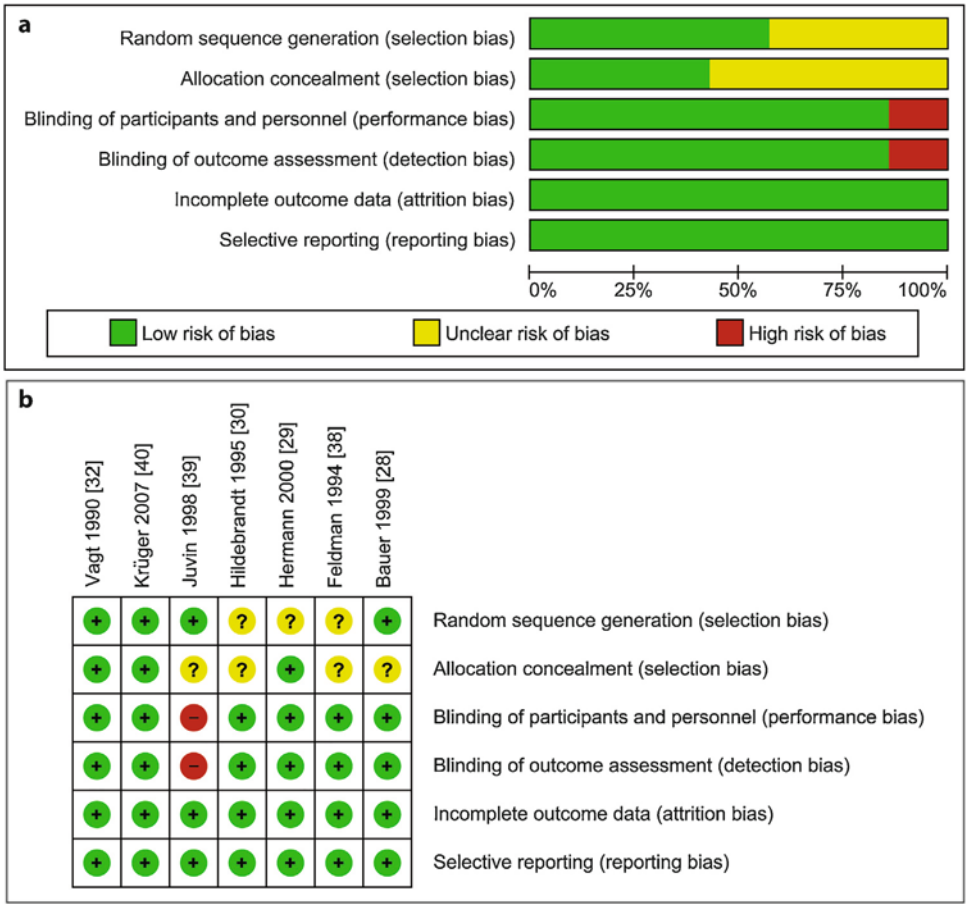

Fig. 2. (a) Risk of bias graph (b) Risk of bias summary.

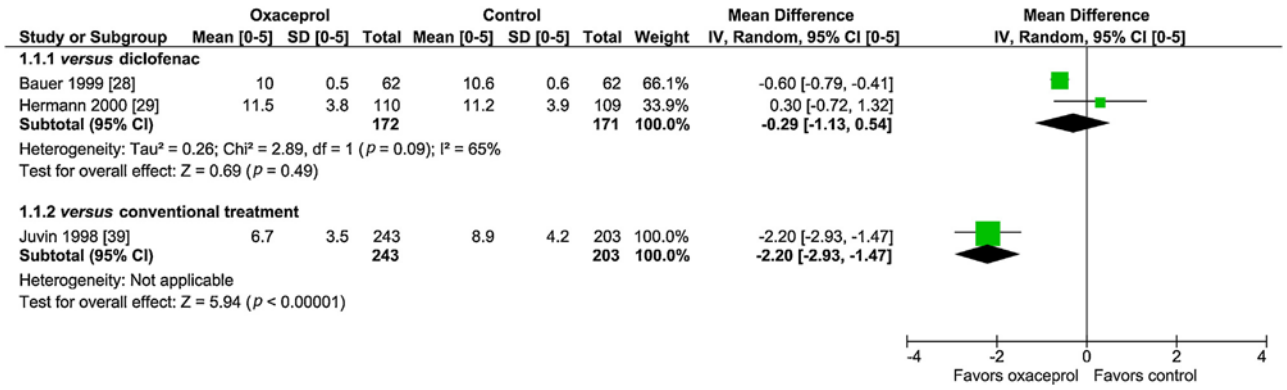

Fig. 3. Lequesne joint function index.

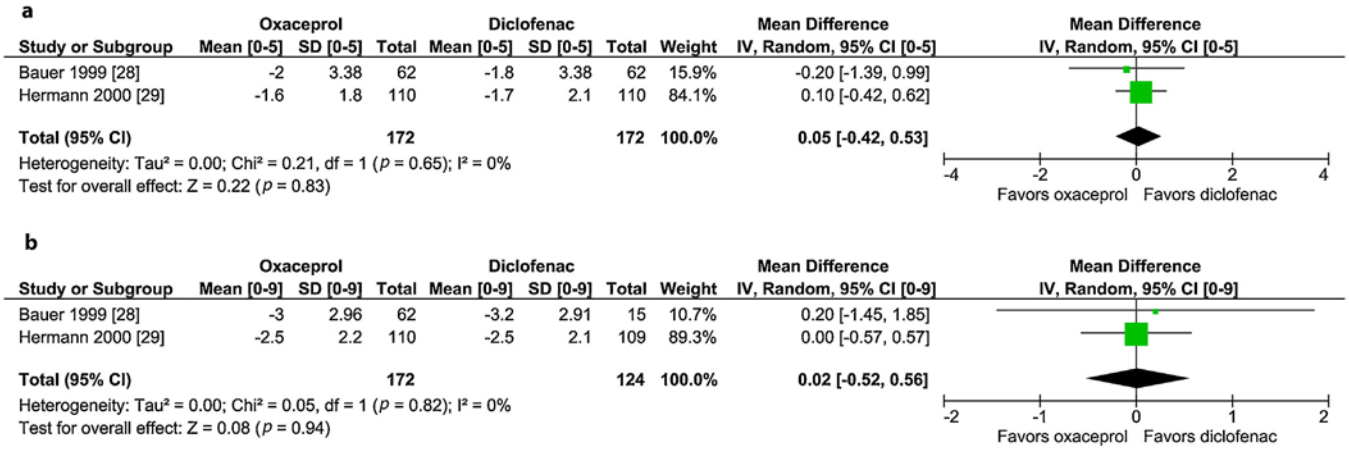

Fig. 4. (a) Pain at rest (b) Weight-bearing pain. Mean values are change from baseline.

Other pain variables

Similar efficacy was observed in: pain during exercise by oxaceprol and ibuprofen [30,32], Fig. S1; weight-relieving pain by oxaceprol and diclofenac [29], Fig. S4. Whereas, oxaceprol significantly reduced: pain in relief position compared to ibuprofen [30], Fig. S1; pain following exercise compared to placebo [40], Fig. S2. Vagt et al. observed significant improvement compared to initial situation during oxaceprol and ibuprofen treatments in the onset of pain with no difference between the groups [32]. Feldman et al. noted 72.7% improvement in pain intensity in patients with OA taking oxaceprol [38]. After one-year of treatment (Fig. S5), visual analogue scale (VAS) pain score significantly ($p < 0.001$) improved in the oxaceprol + CT (32%) group compared to CT (12%) [39].

Global treatment efficacy (Efficacy judgment by investigators/physicians and patients)

The global treatment efficacy, assessed by the investigators/physicians, reported as very good or good was similar in participants treated with diclofenac/ibuprofen (45.5–66.7%) and oxaceprol (45.5–66.6%), Fig. 5. However, the mention "very good" was awarded in 23.3% for oxaceprol and only in 10% for ibuprofen [30]. Similar efficacy judgment was observed by patients: diclofenac/ibuprofen (56.0–63.3%) and oxaceprol (47.0–73.4%), Fig. 5.

NSAIDs as rescue medication

The study by Herrmann and team reported that two patients in the diclofenac group took a few doses of paracetamol (3000 mg/day) as rescue medication [29]. In another study, the use of paracetamol as rescue medication was low with few drop-outs due to lack of efficacy, and there was no significant difference between the groups [40]. The study by Juvin noted that about 50% of the patients were taking NSAIDs at the time of inclusion [39]. During the trial, the number of patients receiving NSAIDs was almost unchanged in the CT group; whereas, depending on the time period compared to baseline, it decreased from 5–11% in oxaceprol + CT group. The one-year cumulative duration of NSAID treatment was significantly reduced (107 *vs.* 152 days; $p = 0.008$) in oxaceprol + CT group compared to CT. Further, the average one-year NSAID consumption (indomethacin) was equivalent to 26 mg/day in CT group, whereas it was only 15 mg/day in oxaceprol + CT group. The decrease in daily consumption significantly favored oxaceprol + CT

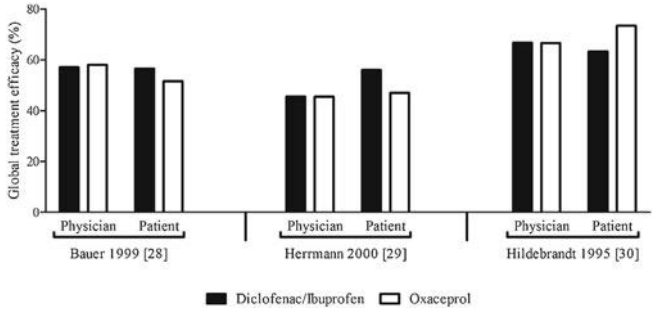

Fig. 5. Global treatment efficacy (judgment by investigators/physicians and patients).

group (p = 0.001). Similarly, the average daily consumption of analgesics (paracetamol equivalent per day) was 567 mg/day in CT group and 515 mg/day in oxaceprol + CT group (p = 0.001) [39]. However, in other two studies, no rescue medication (paracetamol up to 3000 mg daily) intake was reported in patients administered with oxaceprol and diclofenac/ibuprofen [28,32].

Safety and tolerability

Observational and non-randomized studies reported that oxaceprol at 600 mg/day is generally safe [43–50] (Table S3). Further, most of its AEs were dose-dependent [29]; 1200 mg of oxaceprol/day reported with cases, such as GI pain, nausea, skin rash, constipation etc. The meta-analysis data concluded that oxaceprol treatment had numerically less AEs compared to diclofenac (RR, 0.71; 95% CI, 0.45 to 1.11; p = 0.14) and ibuprofen (RR, 0.73; 95% CI, 0.30 to 1.78; p = 0.49); combined effect of oxaceprol *vs.* diclofenac and ibuprofen also showed numerically greater improvement (RR, 0.71; 95% CI, 0.48 to 1.07; $p < 0.1$; data not shown). However, compared to placebo, oxaceprol showed statistically significant reduction in AEs (RR, 0.76; 95% CI, 0.63 to 0.92; p = 0.004), Fig. 6; this data was limited to one study of 153 patients. Feldman et al., in placebo-controlled study, reported a case of vertigo and nausea; vertigo occurring in the oxaceprol group necessitated cessation of treatment. The pain symptomatology and functional state improved in 56% and 25% of patients, respectively, treated with oxaceprol [38]. The frequency of AEs occurring during the trial, accountability to the treatment of OA, was only 5.9% in CT group and 4.9% in oxaceprol + CT group. Digestive disorders were less frequent (3.3% *vs.* 5.4%) with oxaceprol + CT compared to CT group. There was one severe treatment response in each of the two groups: cholestatic hepatitis in CT and gastralgia in oxaceprol + CT. Tolerance over one-year of treatment was judged to be good in 91% and 98% of patients in CT and oxaceprol + CT groups, respectively [39]. The analysis of patients' QoL (EMIR; Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde) did not show any significant evolution of the different components in CT group. In contrast, patients receiving oxaceprol + CT, the physical component improved by 17% in one-year and the difference from CT group was statistically significant (p = 0.001). The improvement of the social and psychological components had remained modest. Overall improvement showed a statistically significant (p = 0.04) difference which favored oxaceprol + CT [39].

Discussion

Systematic reviews are critical tools which summarize a robust overview of a health care intervention for the efficacy (effectiveness in case of real-world study), safety and tolerability [34,51]. Meta-analysis, a key tool in systematic review, allows pooling the results from multiple studies addressing common hypothesis, thus quantifies the known data and recommends the future research that has not been covered adequately in previous research studies [52].

Systematic review of RCTs is traditionally considered as the highest level of evidence for efficacy, safety and tolerability [53,54]. Witte et al., previously, using meta-analysis evaluated the efficacy of oxaceprol in the treatment of OA [55]. The study reported no significant difference between oxaceprol and NSAIDs (two each; diclofenac and ibuprofen). The authors reported that, no RCT was found comparing oxaceprol *vs.* placebo; however, there was a placebo-controlled RCT [38] which was not included for meta-analysis.

The present systematic review, in addition to previous four RCTs *vs.* NSAIDs (two each; diclofenac and ibuprofen), included three other RCTs: two placebo-controlled and a study where oxaceprol was given in combination with CT and compared to CT alone [28–30,32,38–40]. Through this study, the authors updated the efficacy of oxaceprol in the management of OA, as well the overall body of evidence for safety and tolerability. Besides, we have also updated the available data for two on-going RCTs: one each, *vs.* diclofenac and tramadol [41,42].

A total of 1087 patients with OA of the knee and/or hip met the inclusion criteria from seven eligible RCTs. The efficacy, safety and

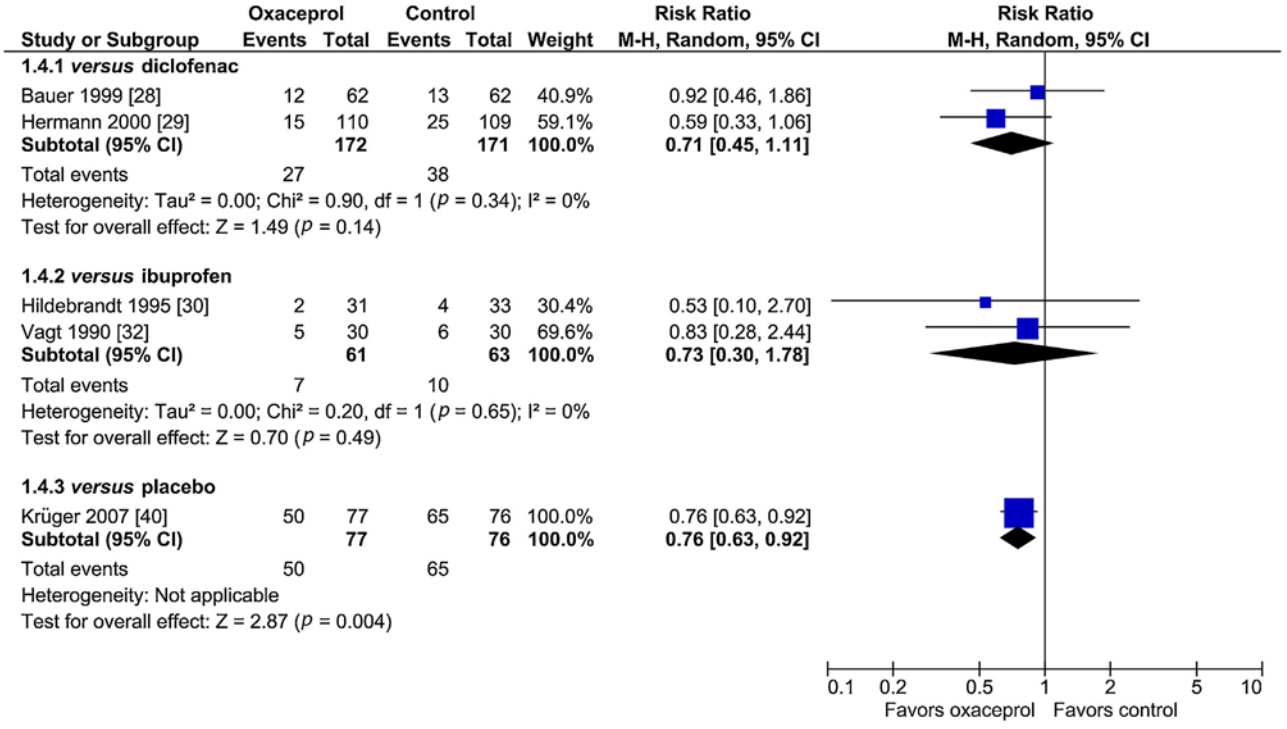

Fig. 6. Safety and tolerability.

tolerability of oxaceprol (200 or 400 mg tid), monotherapy or in combination, was compared with NSAIDs (diclofenac and ibuprofen) and placebo. With evidence from newly included studies, oxaceprol showed equivalent efficacy and a good safety and tolerability profile compared with either diclofenac or ibuprofen treatment. Further, oxaceprol, monotherapy or in combination, demonstrated superior efficacy, safety and tolerability profile *vs.* placebo or CT.

NSAIDs, as diclofenac and ibuprofen, mainly act by inhibiting the synthesis of PGs, thus leading to anti-inflammatory and analgesic activities [56,57]. Whereas, oxaceprol, a derivative from L-proline, acts as an atypical inhibitor of inflammation [58–60]. Oxaceprol acts mainly by inhibiting leukocyte infiltration (adhesion, extravasation and migration) at inflammation sites, thus impeding an early step of inflammatory cascade [25,26,60,61]. This alternative mechanism of action of oxaceprol can explain the observed pain relieving and mobility enhancing actions, as evident from this systematically reviewed and analyzed data. Further, this unique anti-inflammatory activity of oxaceprol makes it devoid of GI AEs; thus, clinically safer in managing OA, especially in patients with confirmed CV or elevated risk of GI AEs. This is further clinically supported from the available real-world evidence (Table S3), besides the eligible trials included in this study.

It is clinically essential to note that in most of the eligible trials, the participants in addition to oxaceprol or active treatment received daily physiotherapy [28–30,32,40]; this highlights the importance of multidisciplinary approach in the management of patients with OA [62]. Further, addition of nutraceuticals such as oxaceprol to existing therapy also improved pain, joint stiffness, mobility, and QoL in OA patients [39,63]. A comparative study, conducted in India, evaluated the therapeutic efficacy and safety of oxaceprol ($n = 35$; 200 mg tid) and oral glucosamine ($n = 35$; 1500 mg od) in OA patients of knee who were on diclofenac (50 mg tid). After 2 weeks of treatment, both the groups showed nearly two-fold increase in pain-free walking time and pain-free squatting. Further, about 66% and 50% of patients, respectively, taking oxaceprol and glucosamine showed improved clinical condition and almost 50% reduction in subjective evaluation of pain by VAS score with comparative safety and tolerance in each group [63]. This further emphasizes the significance of multidisciplinary approach in managing OA, thus helping to prevent the development of more severe form of OA.

With the existing body of clinical evidence, oxaceprol promises to be a good alternative to commonly prescribed NSAIDs for long-term management of patients with OA, as it shows equal efficacy, and better safety and tolerability *vs.* NSAIDs.

Strengths

The present systematic review has several strengths. First, the literature search was performed in majority of guideline recommended databases for identifying both published and grey (unpublished) data. Also, references of included studies were hand-searched for additional trials, if any, which resulted in inclusion of one study. Second, the included literature was not limited to only English language, and included other studies in German and French languages. For therapeutic evaluation of oxaceprol, only parallel-group RCTs were considered leading to minimized differences, at least in terms of clinical study design, for data collection and analysis. Third, wherever statistical pooling was not possible, the available data were systematically reviewed. Further, if possible, estimate was pooled as oxaceprol *vs.* NSAIDs to depict the overall effect of oxaceprol in comparison to NSAIDs. Fourth, across all the included studies, only two doses of oxaceprol (200 or 400 mg, tid) were tested *vs.* diclofenac (25 or 50 mg, tid)/ibuprofen (400 mg, tid), which might have minimized the differences in the evaluated efficacy, safety or tolerability outcomes.

Limitations

Besides the above mentioned strengths, this systematic review has potential limitations. First, with an exception to one study [39], the included studies were of short duration. Second, the statistical pooling was not efficient due to lack of quantitative data across the studies and not all studies reported data for each analyzed outcome. Third, among seven included RCTs, five were conducted in Germany and two in France, which might limit the generalization of results to other countries. However, it is interesting to validate the results of ongoing/completed trials (CTRI/2009/091/000798 and CTRI/2014/08/004821) conducted in other countries with existing data, once published [41,42]. Fourth, the sample size was less than 50 in each group (experimental and control) in three RCTs [30,32,38], which might have decreased statistical power.

Conclusion

The meta-analysis data and systematic review of outcomes showed comparable therapeutic efficacy and better spectrum of safety and tolerability profile of oxaceprol compared to NSAIDs in managing OA. Further, in comparison to placebo, oxaceprol showed superior efficacy, safety and tolerability. However, as the included studies are of small-to-moderate sample size and short duration, additional well-designed RCTs (as well post-marketing surveillance studies) with larger sample size and longer follow-up are desirable for generating sound evidence to further strengthen the use of oxaceprol in managing OA in clinical practice.

Conflict of interest

The authors declare that they have no conflict(s) of interest to disclose. The authors alone are responsible for the content and writing of the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pharep.2018.12.010.

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