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Stephen A. Klinge & Gregory A. Sawyer

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Effectiveness and Safety of Topical Versus Oral Nonsteroidal Anti-inflammatory Drugs: A Comprehensive Review

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Stephen A. Klinge, MD[1]
Gregory A. Sawyer, MD[1]

[1]Department of Orthopaedic Surgery, The Warren Alpert Medical School of Brown University, Providence, RI

Abstract

Introduction: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) represent a relatively recent alternative to oral NSAIDs. Topical NSAIDs are designed to target their therapeutic effect locally to damaged tissue while minimizing systemic exposure. To better inform patients considering topical NSAIDs as an alternative to oral NSAIDs, this is the first comprehensive review to present all available evidence comparing topical NSAIDs with oral NSAIDs in the treatment of both acute and chronic musculoskeletal injury. **Methods:** Six studies, including 600 subjects, compared the use of topical versus oral NSAIDs in the treatment of a variety of acute injuries. Nine trials, including 2403 subjects, studied topical versus oral NSAIDs for chronic injury treatment, almost exclusively for osteoarthritis (OA) of the knee. This review included all available comparative studies, the majority of which were well-designed, double-dummy, placebo-controlled trials. Relevant meta-analyses were also reviewed. **Results:** Topical and oral NSAIDs performed statistically better than placebo for chronic injury treatment. Limited evidence comparing topical NSAIDs with placebo for acute injury treatment was available in the included studies, but supported greater effectiveness for topical NSAIDs. In all head-to-head comparisons, topical and oral NSAIDs demonstrated similar efficacy for treatment of both acute and chronic injuries. There were more gastrointestinal side effects in patients receiving oral NSAIDs, while local skin reactions occurred more frequently in patients treated with topical NSAIDs. **Conclusion:** Overall, topical NSAIDs may be considered as comparable alternatives to oral NSAIDs and are associated with fewer serious adverse events (specifically GI reactions) when compared with oral NSAIDs. Caution should be exercised with the use of both topical and oral NSAIDs, including close adherence to dosing regimens and monitoring, particularly for patients with previous adverse reactions to NSAIDs.

Keywords: nonsteroidal anti-inflammatory drugs; anti-inflammatory; oral; topical

Introduction

The human body mounts an inflammatory response due to tissue damage, including acute musculotendinous strain, chronic joint degeneration, and other injuries. This inflammatory reaction involves dilation of local blood vessels, increased vascular permeability, and local concentration of inflammatory cells and mediators.[1] In the process of clearing damaged tissues, inflammatory cells cause the release of arachidonic acid metabolites, which include the cyclooxygenase (COX) enzymes.[2] One enzyme subtype, COX-1, is also produced continuously throughout the body and coordinates multiple normal cellular processes. These functions include vascular hemostasis, platelet aggregation, and renal blood flow, as well as the formation of a protective mucous lining in the gastrointestinal

Correspondence: Stephen A. Klinge, MD,
Department of Orthopaedics,
593 Eddy St.,
Providence, RI 02903.
Tel: 401-444-4030
Fax: 401-444-6182
E-mail: steveklingemd@gmail.com

(GI) tract. Cyclooxygenase-2 production is induced by the inflammatory response itself, and acts to sensitize pain receptors and recruit inflammatory cells to the site of injury.[3,4]

The earliest type of nonsteroidal anti-inflammatory drugs (NSAIDs) were oral salicylate compounds extracted from willow bark and other plants. These remedies were used since the time of the early Egyptians and the first clinical trial using willow bark was performed in the late 1700s.[5] Since these salicylates were first synthesized and made available commercially in the late 1800s, oral NSAIDs have been the mainstay of treatment worldwide for both acute and chronic musculoskeletal conditions.[5,6] This trend has continued through the introduction of the first modern oral NSAIDs, beginning with indomethacin in the early 1960s.[6] These initial oral formulations are nonspecific NSAIDs that decrease synthesis of both COX-1 and COX-2. It has become clear through widespread use and surveillance that a variety of adverse events are commonly associated with the regular use of nonspecific oral NSAIDs. These effects include an increased risk for bleeding, kidney dysfunction, and GI irritation and ulceration.[3,7] Common contraindications to the use of oral NSAIDs include a history of GI bleeding, kidney or liver impairment, or hypersensitivity to NSAIDs.

To minimize side effects, oral NSAIDs can be administered with various antacid medications or misoprostol. This substance is a prostaglandin analog that protects the gastric mucosa.[8] Cyclooxygenase-2–specific drugs were also developed, which selectively decrease proinflammatory arachidonic acid metabolites while maintaining the gastroprotective effects of COX-1 products. These advances have decreased, but not eliminated, the incidence of significant side effects, including increased rates of stroke and myocardial infarction with some COX-2–specific drugs.[9,10] Today millions take over-the-counter or prescription oral NSAIDs daily, and their use will likely increase given the rising popularity of sports and exercise, the world's aging population, and the ever-increasing prevalence of osteoarthritis (OA).[11–13] Osteoarthritis is a potentially debilitating chronic condition involving joint cartilage degeneration and synovial inflammation and currently affects approximately 30 million Americans.[12] In recent practice guidelines, the American Academy of Orthopaedic Surgeons conditionally recommends routine use of NSAIDs for symptomatic OA of the knee, and the American College of Rheumatology recommends NSAIDs for use in treating knee and hip OA.[14,15]

Topical NSAIDs are nonselective COX inhibitors that have been available on a nonprescription basis in Europe and Asia for several decades, but were first approved for OA by the US Food and Drug Administration in 2007.[16,17] These medications specifically target absorption to injured tissue, whereby minimizing systemic exposure. This targeting was designed to decrease rates of associated side effects while still providing relief of pain and inflammation.[18] Administration of topical ketoprofen or ibuprofen has been shown to result in plasma drug concentrations $>$ 99% lower compared with similar amounts of the oral form.[19–21] At the same time, multiple studies have demonstrated topical NSAIDs to be comparably well absorbed into local tissues compared with oral NSAIDs, with even higher local tissue concentrations in certain areas, including subcutaneous tissue, cartilage, and meniscus, while exhibiting $\geq$ 90% reductions in peak systemic concentrations.[21–23]

However, considerable controversy remains regarding the efficacy of topical NSAIDs. The present study offers the first comprehensive review of all clinical trials and meta-analyses comparing the efficacy and safety of oral NSAIDs compared with topical NSAIDs. Our goal is to clarify the potential benefits and limitations of topical NSAID delivery for the most commonly used NSAIDs worldwide for a variety of acute and chronic musculoskeletal conditions.

Materials and Methods

To identify all comparative clinical trials and meta-analyses analyzing topical versus oral NSAIDs, a search of PubMed was performed (1950 to October 1, 2012) using the keywords *non-steroidal*, *anti-inflammatory*, *NSAID*, *injury*, *musculoskeletal*, *pain*, *arthritis*, *topical*, *gel*, *cream*, *solution*, *spray*, and *plaster*. Additional references were retrieved from the Cochrane library database and other published reviews and meta-analyses. Clinical studies or meta-analyses that analyzed the use of salicylate medications were excluded because these drugs have failed to demonstrate significant efficacy against joint pain and OA.[16] All studies were carefully reviewed for relevant information, including subject characteristics, study design, dosing regimens, clinical efficacy, and side effects.

A total of 6 trials comparing treatment of acute injuries[24–29] and 9 studies analyzing chronic treatment[30–38] were identified, as well as 4 meta-analyses that reviewed a subset of the 15 included trials.[39–42] All studies compared topical and oral therapies. To maintain double blinding, most studies used a double-dummy placebo design in which both groups

received an active medication along with a corresponding placebo form. Additionally, because "placebo control" of the double-dummy design requires an all-placebo comparison group, a number of trials also included such comparison arms.

Studies are presented in different sections stratified by acute versus chronic treatment, injury or type of arthritis treated, and drug type (in the case of diclofenac, as multiple similar trials were conducted using that medication to treat knee OA). Additionally, well-designed randomized controlled trials (RCTs), defined as those with an Oxford Quality Score of ≥ 3/5, considered relatively free of bias, are reviewed first and highlighted for the reader.[43] Trials with quality scores < 3/5 that have not previously been included in systemic reviews and meta-analyses, typically for lack of blinding, randomization, or placebo control, are also analyzed.

In all trials reviewed, comparison groups were statistically similar in terms of demographics and baseline characteristics. In double-dummy RCTs, which represent the majority of studies presented in this article, participants received placebo formulations as indistinguishable pills or topical preparations that were administered in the same manner as the active medications. All trials had relatively similar exclusion criteria, which generally included any history of hypersentivity to NSAIDs; GI bleeding or ulceration; significant kidney, liver, or cardiac disease; bleeding disorder; asthma or bronchospasm; pregnancy or lactation; malignancy; or concomitant anticoagulant use. Trials also excluded subjects with a history of crystalline, inflammatory, traumatic, or other secondary types of arthritis and attempted to control for confounding concomitant injury treatment with various additional exclusion criteria. Studies either restricted the use of oral or topical NSAIDs during the previous 1 to 4 weeks or used a washout period of ≤ 7 days. Furthermore, trials excluded participants who had recent corticosteroid treatment (ie, oral treatment within weeks or intra-articular injections within months), viscosupplementation injection within several months, or major joint surgery within the past 6 months.

Participants in acute-treatment trials presented within several days of injury onset. Subjects in chronic treatment trials were middle-aged to elderly subjects with active and at least mildly to moderately symptomatic OA, and disease was usually confirmed by recent radiographs. Otherwise, important trial details not mentioned in the body of the text, including demographic information, specifics regarding treatment regimens, and complete rates of side effects are outlined in Tables 1 and 2. When reported, rates of total side effects and GI and local skin reactions are presented separately.

Description of Clinical Trials

Acute Injury

General Sports/Overuse Injury

Four trials, with a total of 309 participants, evaluated the efficacy of NSAIDs for the treatment of acute sports and overuse injuries. In a double-dummy RCT, Akermark and Forsskåhl[24] compared 62 outpatients in a sports medicine clinic who had various conditions, the most common being Achilles peritendinitis, iliotibial band friction syndrome, and epicondylitis. Twenty-one subjects received topical indomethacin spray while 20 others received oral indomethacin. Twenty-one additional subjects received both placebo formulations. At 1 week, 48% of the topical group and 25% of the oral group reported "marked or symptom-free" improvement, compared with 14% in the all-placebo arm. Percentages at 2 weeks were 80%, 65%, and 52%, respectively. These response rates were similar among groups, including those who received both placebo formulations. However, subjects who received the active topical preparation had higher self-perceived improvement scores on days 3 and 7, as well as improved "pain in connection with daily activity" by day 7 compared with the all-placebo arm ($P < 0.05$). Overall, 35% of topical versus 43% of oral indomethacin subjects reported side effects, and GI events represented 9% versus 17% of those reactions, respectively. Local skin reactions (ie, redness, maculopapular rash) occurred in 17% of topically treated participants, with no skin reactions in the oral group.

Whitefield et al[25] conducted a double-dummy RCT of soldiers treated within 24 hours for assorted soft tissue injuries, including strains of the ankle, knee, and shoulder. Participants received either gel or oral ibuprofen formulations. After ≥ 1 week of treatment, the percentage of subjects rating themselves as "completely better" was similar (48% vs 60%). Furthermore, secondary outcomes were comparable and treatment was rated as excellent by 60% of topically versus 71% of orally treated subjects. A total of 6 participants experienced side effects, none of which were determined to be study related.

Martens[26] conducted a randomized but non-blinded, non–placebo-controlled study of subjects presenting with acute soft tissue injuries. The most common injuries were epicondylitis and supraspinatus strains as well as assorted types of tendinitis. Over 2 weeks, 56 participants received flurbiprofen via patches and 52 oral diclofenac. Subjects treated with topical NSAIDs had statistically improved pain and tenderness severity compared with those receiving the oral formulation ($P < 0.05$), and participants

Table 1. Topical Versus Oral NSAIDs: Acute Injury

Author	Low-Bias RCT[a]	Subject Demographics (Topical/Oral)			Topical Regimen	Top Form	Oral Regimen	Results (Topical vs Oral)	Follow-up	Side Effects (Topical vs Oral[f])		
		N	Mean Age ± SD/Range	M:F						Total	GI	Skin
Sports/Overuse Injuries												
Akermark and Forsskåhl[24]	Yes	21/20[c]	30 (18–24)/ 32 (16–52)	2.3:1/ 3:1	Indomethacin TID	Spray (3–5)	25 mg indomethacin TID	Similar, 80% vs 65% "marked/ symptom-free" improvement	14 days	35 vs 43	9 vs 17	17 vs 0
Whitefield et al[25]	Yes	50/50	26 (19–50)/ 25.5 (18–38)	24:1/ 15.7:1	5% ibuprofen TID	Gel (60–70g)	400 mg ibuprofen TID	Similar, 48% vs 60% "completely better"	7–14 days	None (study-related)	None (study-related)	None (study-related)
Martens[26]	No[b]	56/52	40.6 (15–74)/ 43.9 (18–76)	0.8:1/ 1.2:1	Flurbiprofen BID	Patch (40 mg)	50 mg diclofenac BID	Topical superior, 92% vs 73% "improved"[e,g]	14 days	14 vs 17	Oral higher[g]	Topical higher
Vanderstraeten and Schuermans[27]	No[b]	30/30	> 14 years (No difference between groups)	No difference	10% etofenamate TID	Cream (5-cm strand)	275 mg naproxen TID	Similar, 65% vs 86% no/mild pain	14 days	3 vs 20	0 vs 20	3 vs 0
Ankle Sprain												
Cesarone et al[28]	No[b]	16/14[d]	46.7 ± 4.5/ 47 ± 6.3	2.2:1/ 6:1	10% ketoprofen TID	Spray (5–6)	25 mg ketoprofen TID	Topical superior improvement in activity pain and tissue swelling[g]	7 days	0 vs 21	0 vs 21	None
Low Back Pain												
Hosie[29]	Yes	124/ 137	37.4 (18–63)/ 37.9 (18–62)	1.2:1/ 1.1:1	3% felbinac TID	Foam (2 g)	400 mg ibuprofen TID	Similar, 92% vs 90% "fair to excellent" efficacy	14 days	16 vs 14	10 vs 7.5	< 1 vs 2

[a]Double-dummy randomized, controlled trial with Oxford Quality Score ≥ 3/5.
[b]Nonrandomized, non-blinded, and/or non–placebo-controlled trial.
[c]21 additional subjects received both placebo formulations.
[d]11 subjects comprised an untreated comparison group.
[e]Did not use intention-to-treat analysis.
[f]Percentage of subjects with topical vs oral side effects.
[g]Statistically significant.
Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized controlled trial; SD, standard deviation.

in the oral group required statistically greater amounts of acetaminophen as rescue medication ($P < 0.05$). In addition, looking only at subjects who completed a full 2 weeks of treatment (not intention to treat), 92% of topical subjects were statistically "improved" per investigator assessment compared with 73% in the oral group (primary outcome), and topical participants also had statistically reduced clinical condition severity ($P < 0.05$). There were statistically more GI side effects in the oral group ($P = 0.011$), causing 2 subjects to withdraw. The majority of topically treated subjects with adverse events experienced mild local skin reactions and 1 withdrew due to that issue.

Vanderstraeten and Schuermans[27] conducted a non-blinded, non–placebo-controlled trial studying 60 subjects with acute soccer injuries who received either etofenamate cream or oral naproxen. Outcomes were similar as 65% had no/mild pain in the topical group versus 86% in the oral group at the end of the 14-day treatment period. There were fewer side effects in the topical compared with the oral group (3% vs 20%). Two patients in the oral and 1 patient in the topical group dropped out due to significant GI side effects.

Table 2. Topical Versus Oral NSAIDs: Chronic Injury

Author	Low Bias RCT[a]	Subject Demographics (Topical/Oral)			Topical Regimen	Top Form	Oral Regimen	Results (Topical vs Oral)	Follow-up	Side Effects (Topical vs Oral[j])		
		N	Mean Age ± SD/ Range	M:F						Total	GI	Skin
Knee OA/ Diclofenac												
Sandelin et al[30]	Yes	124/78[c]	61 ± 8.3/ 61 ± 7.9	0.6:1/ 0.4:1	1% diclofenac TID	Gel (3 g)	50 mg diclofenac BID	Similar improvement (vs all-placebo)[i,k]	2-4 weeks	27 vs 24	5 vs 13	13 vs 1[k]
Tugwell et al[31]	Yes	303/301	64 ± 10/ 63 ± 10	0.8:1/ 0.8:1	1.5% diclofenac TID	Sol (50 drops)	50 mg diclofenac TID	Similar, 66% vs 70% "responders"	12 weeks	Not reported	35 vs 48[k]	50 vs 5[k]
Simon et al[32]	Yes	154/151[d]	61.7 ± 9.8/ 62 ± 10.5	0.5:1/ 0.6:1	1.5% diclofenac QID	Sol (40 drops)	100 mg diclofenac (SR)[g] QD	Similar improvement (vs all-placebo)[k]	12 weeks	62 vs 62	7 vs 24	27 vs 7
Knee OA/Other NSAIDs												
Dickson[33]	Yes	117/118	63 ± 11/ 62 ± 12	0.6:1/ 0.5:1	Piroxicam TID	Gel (1g)	400 mg ibuprofen TID	Similar 64% vs 60% "excellent/ good" response	4 weeks	27 vs 22	13 vs 9	3 vs 2
Rother et al[34]	Yes	138/132[e]	63.3 ± 10.1/ 62.4 ± 9.6	0.8:1/ 0.6:1	Ketoprofen BID	Gel (4.8 g)	100 mg celecoxib BID	Similar, 47% vs 39% "good/ excellent" (vs all-placebo[k])	6 weeks	54 vs 50	9 vs 14	28 vs 20
Underwood et al[35]	No[b]	144/138	63 (56–69)/ 63 (56–68)	0.8:1/ 1:1	1500 mg ibuprofen/ day (max)	Gel	1200 mg ibuprofen/ day (max)	Similar outcomes	12 months	56 vs 56	40 vs 42	None reported
Tiso et al[36]	No[b]	9/10	58.9 ± 10.3/ 57 ± 7.9	0:9/ 0.3:1	4% ibuprofen QID	Gel (2 mL)	800 mg ibuprofen TID	Similar improvement	2 weeks	None reported	None reported	None reported
Doi et al[37]	No[b]	87/78	66.1 ± 9.9/ 67.2 ± 9.4	0.4:1/ 0.4:1	Various topical NSAIDs[f]	Plaster	Various oral NSAIDs[h]	Similar improvement	4 weeks	0 vs 3	0 vs 1	None reported
Hand OA												
Zacher et al[38]	Yes	165/156	60.7 ± 9.4/ 63.2 ± 9.4	0.2:1/ 0.1:1	Diclofenac QID	Gel (10-cm strand)	400 mg ibuprofen TID	Similar, 40% vs 34% pain "responders"	3 weeks	22 vs 27	9 vs 14	None reported

[a]Double-dummy, randomized, controlled trial with Oxford Quality Score of ≥ 3/5.
[b]Non-randomized, non-blinded and/or non-placebo-controlled trial.
[c]79 additional subjects received both placebo formulations.
[d]Study included 2 placebo groups and a double-active treatment group.
[e]127 patients received both placebo treatments.
[f]Received either topical BID flurbiprofen (40 mg), indomethacin (70 mg), or ketoprofen (30 mg).
[g]Sustained-release.
[h]Received either oral BID loxoprofen (60 mg), diclofenac (25 mg), or zaltoprofen (80 mg), all with antacid.
[i]In subgroup analysis of subjects with baseline scores above median.
[j]Percentage of subjects with topical vs oral side effects.
[k]Statistically significant.
Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized controlled trial; SD, standard deviation.

Ankle Sprain

Cesarone et al[28] studied the treatment of acute ankle sprains in subjects with chronic venous disease. The trial was nonrandomized, non-blinded, and non–placebo-controlled, although it included an untreated comparison group. Sixteen participants received topical ketoprofen spray, 14 received oral ketoprofen, and 11 were untreated. Treatment lasted 1 week and included therapy with a light elastic bandage

for all participants. At study completion, the topical group had significantly less activity pain and soft tissue thickness compared with oral and untreated subjects ($P < 0.05$). Additionally, topically treated participants improved by 39 percentage points on a treadmill walking test versus 18 points in the other groups (> 10% difference needed to discriminate between treatment effects). Few side effects were reported, and included heartburn in 3 orally and 2 untreated participants.

Low Back Pain

Hosie[29] studied 261 subjects with acute low back pain in a multicenter, double-dummy RCT. Participants received either a foam formulation of felbinac or oral ibuprofen for up to 2 weeks. Severity of symptoms was similar among groups at the study conclusion, but both groups demonstrated a statistical improvement from baseline ($P < 0.001$). Overall assessment of efficacy was similar ("fair to excellent" in 92% of topically vs 90% of orally treated subjects). Although total adverse events rates were similar, GI reactions were more often moderate or serious in orally treated participants. Furthermore, no GI reactions were deemed definitely drug related in topically treated subjects, with several participants reporting them after taking oral placebo.

Interpretation of Acute Treatment Trials

A total of 6 trials that included 600 subjects compared 7 to 14 days of topical versus oral NSAIDs for treatment of various acute injuries. More than two-thirds of subjects were in well-designed, double-dummy RCTs. Limited evidence from this review suggests that topical NSAIDs are more effective than placebo for the treatment of acute injuries. Topical indomethacin significantly improved pain and self-perceived improvement scores.[24] Strong evidence from this review supports the notion that topical NSAIDs are at least as effective as oral NSAIDs for the treatment of acute musculoskeletal injuries. Subjects treated with topical NSAIDs experienced similar outcomes in 4 of 6 trials[24,25,27,29] and statistically improved outcomes compared with orally treated participants in 2 of 6 trials.[26,28] Three of the 4 studies that demonstrated similar clinical outcomes were un-biased, double-dummy RCTs.[24,25,29] The 2 trials that demonstrated statistically improved pain, tenderness, or extremity swelling were not RCTs.

Reported rates of GI side effects were higher in orally (0%–21%) compared with topically treated groups (0%–10%) and there was a statistically higher likelihood of GI events with oral treatment in 1 trial.[26] Skin reactions were more likely in topically versus orally treated subjects (0%–17% vs 0%–2%), but differences were not statistically significant and the events associated with topical NSAIDs were generally minor.

The most effective topical NSAIDs, with limited evidence of improved outcomes versus oral preparations, were the flurbiprofen patch and ketoprofen spray.[26,28] The foam, gel, and cream formulations demonstrated similar outcomes compared with oral NSAIDs.[24,25,27,29] Overall, for the treatment of acute injuries, topical NSAIDs are at least as equally effective as oral formulations, with some evidence of improved outcomes with patches and sprays.

Mason et al conducted a meta-analysis that analyzed the trials by Hosie (low back pain [felbinac foam vs oral ibuprofen]), Whitefield et al (assorted strains [gel vs oral ibuprofen]), and Akermark and Forsskåhl (tendinitis [spray vs oral indomethacin]) and found statistically similar overall success rates (57% for topical vs 62% for oral treatment).[24,25,29,39] A recent Cochrane review, looking at the same trials, found insufficient data to perform a meta-analysis.[41]

Chronic Injury

Knee OA

Eight trials compared the use of topical versus oral NSAIDs in subjects with mild-to-moderate active arthritis of the knee, 5 of which were double-dummy RCTs.

Knee OA/Diclofenac

In the 3 trials comparing topical versus oral diclofenac, subjects with knee OA were administered either active topical or oral diclofenac along with a corresponding placebo formulation in classic double-dummy RCT fashion. In addition, 2 of the 3 studies included all-placebo comparison arms, in which a group of subjects received both inactive formulations (topical and oral). Two of 3 trials used similar outcomes measures, including the Western Ontario and McMaster Universities Arthritis Index (WOMAC).[30–32]

Sandelin et al[30] compared 124 subjects who received topical (gel) and 78 subjects who received oral diclofenac. While each active treatment group received the standard corresponding placebo formulation, a third group of 70 participants received both placebo formulations. Overall, there was no significant difference in visual analog scale (VAS) pain scores or index of severity for knee OA scores after 2 and 4 weeks in any of the groups, including placebo. However, when a subgroup analysis was performed for subjects with baseline scores above the median, subjects in the oral and topical groups both demonstrated similar statistically

improved index of severity for knee OA scores compared with placebo ($P < 0.05$). There was a statistically greater likelihood of skin reactions with topical versus oral treatment, with twice as many compared with placebo ($P < 0.01$). Gastrointestinal side effects were statistically similar when comparing the topical versus placebo groups, but were 2 to 3 times more likely in the oral group ($P = 0.09$). One subject withdrew from the oral group due to abdominal pain, 3 from the topical group because of local skin reactions, and 2 from the placebo group because of skin reactions.

Tugwell et al[31] compared 303 topically versus 301 orally treated subjects. Topical diclofenac was administered as a solution via a dropper. The number of responders in each group was similar (66% vs 70% at up to 12 weeks). On intention-to-treat analysis, the oral group demonstrated statistically greater improvement in only 1 WOMAC category (physical function) compared with the topical group ($P < 0.01$). Topically treated subjects had statistically fewer GI events ($P < 0.001$) and significantly fewer dropped out due to GI complaints compared with orally treated subjects ($P < 0.0001$). There was also a statistically higher incidence of asthma and dizziness as well as laboratory abnormalities in the orally treated group. These laboratory changes included an increased likelihood of developing elevated liver enzymes, decreased hemoglobin levels, or reduced creatinine clearance ($P < 0.05$). However, topically treated subjects were statistically more likely to have local skin reactions ($P < 0.001$) and drop out the trial due to these events ($P < 0.0001$). All skin reactions resolved rapidly after drug cessation.

Simon et al[32] compared treatment with diclofenac topical solution (drops) in 154 subjects with oral diclofenac treatment in 151 others for 12 weeks. The study was a double-dummy RCT that also included 3 other comparison groups. One additional arm was given both placebo formulations, another received the topical carrier compound without active drug as well as the oral placebo, and a fifth group of subjects received both active treatments. Outcome measures included the WOMAC index. Results revealed no difference between topical and oral treatment groups, which were both statistically improved compared with the placebo groups ($P < 0.05$), while the arm receiving both active drugs experienced no added benefit. Rates of local skin reactions were higher in the topical diclofenac group and 5 subjects withdrew due to these events. Adverse GI reactions were more common in the oral treatment arms, while the rate of GI events in the topical group was similar to that in the all-placebo group. Participants who received both active medications had no additional risk of GI events. Compared with the topically treated group, more subjects treated with the active oral formulation developed laboratory abnormalities, including decreased hemoglobin levels, elevated alanine aminotransferase/aspartate aminotransferase levels, or elevated creatinine levels.

Knee OA/Non-Diclofenac

Five additional trials, including 2 double-dummy RCTs, studied subjects with knee OA who were administered NSAIDs other than diclofenac. Dickson[33] compared 117 subjects who were given topical piroxicam gel with 118 who were treated with oral ibuprofen in a double-dummy RCT. After 4 weeks of treatment, outcomes assessed included pain perception, mobility in daily living, and supplemental analgesia required (acetaminophen). Efficacy outcomes measures were similar, including amounts of rescue medication used. Comparing topical versus oral groups, 64% versus 60% of subjects exhibited an excellent or good response. Physician-judged response rates were also equivalent (56% vs 57%, respectively). There were similar rates of both GI and skin reactions and numbers of participants withdrawing due to these events.

Rother et al[34] compared 138 subjects who received ketoprofen gel with 132 who were treated with oral celecoxib in another double-dummy RCT. One hundred twenty-seven participants who received both placebo formulations were also included. Forty-seven percent of topical versus 39% of oral subjects had a "good/excellent" response after 6 weeks of treatment, with both rates being statistically superior to placebo ($P < 0.05$). The WOMAC was the primary outcome measure. Gastrointestinal side effect rates were similar in the topical and all-placebo group but higher in the oral arm. More local skin reactions were reported in the topical group.

Three other non–placebo-controlled trials studied the effects of topical versus oral NSAIDs for the treatment of knee OA. Two of 3 studies compared topical versus oral ibuprofen. Underwood et al[35] randomized 144 subjects to ibuprofen gel and 138 to oral ibuprofen. At 12 months, this multicenter, non-blinded, open-label trial had the longest follow-up period of all included trials. As part of the design, subjects were encouraged to use topical or oral ibuprofen, but also allowed to use various other types of analgesics prescribed by general practitioners. Changes in WOMAC scores were similar at 1 year and no differences in secondary outcomes were observed. Both groups had similar low rates of serious adverse events. However, a statistically greater number of subjects taking oral ibuprofen had other systemic events. These reactions included a defined respiratory event,

17% versus 10% (95% CI of difference, –17% to –2.0%), and average increase in serum creatinine level (95% CI, 0.9–6.5) versus topically treated participants. In addition, 11% of orally treated subjects changed treatment due to adverse effects compared with just 1% in the topical group ($P < 0.05$).

Tiso et al[36] conducted a randomized, prospective, but non-blinded comparison trial in which 9 participants were given ibuprofen gel and 10 oral ibuprofen. Improvements using the WOMAC and 12-Item Short Form Health Survey outcome measures were similar at 4 weeks. No side effects were reported.

Finally, Doi et al[37] conducted a randomized, open-label study comparing the use of various topical NSAIDs applied in a plaster form to the knee of 87 subjects with various oral NSAIDs administered to 78 participants. After 4 weeks, the groups showed similar improvement using the Japanese Knee Osteoarthritis Measure and a pain VAS. Only 1 GI side effect was reported in the oral group, although all subjects given oral NSAIDs were also administered some form of acid reduction medication concomitantly.

Hand OA

One trial studied OA of the hand. Zacher et al[38] analyzed symptomatic finger joint arthritis in subjects with moderate baseline pain in a multicenter, double-dummy RCT. One hundred sixty-five subjects treated with diclofenac gel were compared with 156 subjects treated with oral ibuprofen for 3 weeks. A similar number of subjects (40% vs 34%) displayed > 40% improvement (predetermined significance) in pain intensity. There were more severe side effects in the ibuprofen group (6%) compared the topical group (2%). Orally treated participants had more total side effects. Comparing orally versus topically treated subjects, more withdrew overall due to adverse drug reactions (13 vs 2), specifically GI reactions (8 vs 1).

Interpretation of Chronic OA Trials

Nine trials comprising 2403 subjects compared the use of topical and oral NSAIDs for the treatment of chronic OA for 2 weeks up until 12 months. Eight of 9 trials studied OA of the knee. There is strong evidence that both topical and oral NSAIDs are more effective than placebo based on finding from 3 RCTs.[30,32,34] Topical NSAIDs are also as effective as oral NSAIDs for the treatment of chronic OA. This conclusion is based on findings across all 9 trials,[30–38] including 6 well-designed, double-dummy RCTs that comprised 80% of total study participants.[30–34,38] Diclofenac was the most common single medication compared.[30–32]

Gastrointestinal side effects were more commonly encountered with administration of oral NSAIDs, with rates > 10% in two-thirds of trials,[30–32,34,35,38] and statistically higher in the largest trial included.[31] Local skin reactions were more common in topically treated subjects, with rates > 10% in 44% of studies[30–32,34] and statistically higher in 2 large trials.[30,31] However, GI reactions with oral NSAIDs tended to be more serious and more often led to study withdrawal. Conversely, skin reactions with topical NSAIDs were generally minor and resolved quickly after drug cessation. Subjects given oral NSAIDs in several trials were also more likely to experience other potentially serious systemic adverse reactions (eg, respiratory events, elevations in liver/kidney laboratory parameters and reductions in hemoglobin levels).

Almost all trials used gel or solution preparations of NSAIDs, and both formulation types were similarly effective. Overall, for chronic OA, topical NSAIDs are similarly effective compared with oral NSAIDs and have a more benign side effect profile. A recent Cochrane meta-analysis, which included a subset of the studies reviewed above,[32,33,34,38] reported an overall 55% versus 54% successful treatment rate when comparing topical and oral NSAIDs.[42] The review also reported that overall GI side effect rates were 17% compared with 26%, and local skin reactions occurred at a rate of 22% compared with 6%. The percentage of subjects who withdrew due to adverse events was 12% compared with 15%.[42] Another meta-analysis including a smaller subset found an equal 37% success rate comparing topical with oral treatments, and systemic adverse events and withdrawals did not differ.[40]

Discussion

All available clinical trial data examining the use of topical versus oral NSAIDs for acute and chronic injury were analyzed in this review, and included 600 acute and 2400 chronic treatment subjects, respectively. The majority of included studies were unbiased and well-designed, double-dummy RCTs. For the treatment of acute injuries, a meta-analysis by Mason et al[39] found that topical NSAIDs were statistically more effective than placebo in 19 of 26 trials analyzed. In this current review, subjects who received topical NSAIDs had superior efficacy compared with placebo in the one available double-dummy RCT.[24] Otherwise, all 6 head-to-head comparison trials demonstrated that topical NSAIDs are as effective as oral regimens for the treatment of acute injuries.[24–29] Forty percent of trials actually had

statistically superior outcomes for topical versus oral treatment, but neither was an RCT.[26,28] Therefore, while superior to placebo, there is only limited evidence to support the superiority of topical versus oral NSAIDs for acute injuries.

For the treatment of chronic OA, topical NSAIDs are clearly more effective than placebo. All 3 large RCTs that included all-placebo comparison groups demonstrated statistically better outcomes for topical and oral treatment.[30,32,34] When compared, topical NSAIDs were as effective as oral NSAIDs for the treatment of OA. All 9 head-to-head chronic trials included in this analysis demonstrated comparable efficacy.[30–38] The evidence of treatment efficacy is by far strongest for OA of the knee (8/9 chronic trials; $>$ 2100 participants). In addition, topical diclofenac was the best single medication studied (3 RCTs with $>$ 1100 subjects).[30–32]

Different NSAIDs with various formulations (eg, gel, solution, patch, and spray) were administered in trials included in this analysis. For acute injury treatment, patches and sprays demonstrated statistically superior effectiveness over oral NSAIDs (both trials not RCTs),[26,28] while outcomes for gels, foams, and creams were similar to oral treatment.[24,25,27,29] For chronic injuries, no differences between the effectiveness of solutions or gels administered were found. Patches and sprays may be able to create higher local tissue concentrations compared with gels and other formulations, and these concentration differences may affect the relative efficacy of NSAIDs, particularly for acute injury treatment.[21–23] In addition to the drug vehicle, the improved efficacy for some formulations of NSAIDs could also be due to the drug itself. Ketoprofen, for example, has previously been shown to exhibit higher skin permeability compared with the other topical formulations of NSAIDs, particularly with a patch as the form of delivery.[44] Based on the available evidence, spray and patch formulations, if available, are recommended over other preparations to maximize effectiveness, especially for acute injury treatment. However, more randomized head-to-head clinical comparisons are needed to fully address the relative effectiveness of various topical preparations of NSAIDs. Of note, topical formulations currently approved by the US Food and Drug Administration include various forms of topical diclofenac, including Flector® (patch), Pennsaid® (solution), Solaraze® (gel), and Voltaren® (gel).[45]

Gastrointestinal side effects have been a limiting factor in the use of oral NSAIDs.[46,47] Overall, these 15 reviewed studies revealed that GI side effects occurred far less frequently for topically treated subjects, with significantly higher rates in oral arms found in several studies.[26,31] Of note, GI event rates were very low in topically treated groups in the acute-injury trials and equal to rates observed in the all-placebo comparison groups in OA trials.[30,32,34] Rates of serious GI events leading to drug cessation were also much higher in orally treated participants. Another author previously showed that 22% to 68% of patients given chronic oral NSAIDs ultimately developed mucosal erosions, peptic ulceration, perforation, or bleeding.[47] In contrast, no significant association has been linked to the use of topical NSAIDs.[48,49] Compared with topically treated subjects, participants receiving oral NSAIDs in this review were also much more likely to have other potentially serious systemic side effects. These reactions included respiratory events, decreases in hemoglobin levels, or elevations in liver or kidney function tests. Much higher plasma drug concentrations observed after oral versus topical administration of various NSAIDs seem to account for these higher rates of GI and other systemic effects.[19–23]

It is also clear in this analysis that local skin reactions were much more common in those treated topically and statistically higher in several studies.[30,31] However, 2 large meta-analyses of placebo-controlled trials demonstrated an overall 4% to 6% rate of local reactions in both active and topical placebo groups.[39,40] In the trials outlined above, local skin reactions were generally mild, and all resolved quickly after drug discontinuation. To minimize application-site reactions for the treatment of acute injuries, gel and cream formulations are recommended as first-line NSAIDs. Rates of local skin reactions were low with these preparations compared with spray and patch formulations.[25,27,29] For the treatment of chronic injuries, gel formulations are recommended over solution preparations to minimize skin reactions. Sixty-seven percent of trials that used gel preparations reported low rates of skin side effects in chronic trials.[33,35–38] Two trials using gels had skin reaction rates of 13% to 28%.[30,34] While overall there were statistically more application site reactions in the study by Sandelin et al,[30] a similar number of subjects withdrew from both topical gel and placebo groups due to these skin reactions. In the 2 studies that used solution drops, rates of application site reactions were higher, ranging from 27% to 50%, but only 3% to 5% of subjects withdrew due to these reactions.[31,32]

It should be noted that there were relatively few serious side effects in any group, but all trials excluded subjects at high risk for reactions. This included participants with any history of hypersentivity to NSAIDs; GI bleeding or ulceration; significant kidney, liver, cardiac, or lung disease; or

other risk factors. While far less likely to cause GI and other reactions, prospective patients who have previously had GI reactions with the use of oral NSAIDs or those who are prone to skin reactions should be careful when considering topical NSAIDs. Users should adhere closely to application directions, monitor themselves for reactions, and always tell their doctor about their potential use of particular NSAIDs. It should be noted that a number of large OA treatment trials included in this analysis had relatively high total side-effect rates as well, ranging from 27% to 62%.[24,30,32–35] However, adverse event rates were similar when active drug versus all-placebo groups were compared in 3 of 4 trials that had such comparison arms.[24,30–32] This highlights the fact that a number of patients react adversely to placebo formulations and complicate the analysis of side effects experienced during treatment with NSAIDs.

Findings from this review and previous meta-analyses continue to support the efficacy of topical NSAIDs. Some of the previous doubt and criticism stemmed from inadequately comparing topical drugs with placebo alone, using poor trial design, and using unvalidated or unresponsive outcome measures.[31,50] All trials included in this article were direct topical versus oral comparative studies, and the majority were highly rated double-dummy RCTs, and a number also had the added benefit of all-placebo comparison groups. The majority of trials used well-known and validated outcome measures, most notably the WOMAC index. However, short duration of follow-up is still a limitation for OA treatment trials, as the majority of trials in this review had treatment periods of 2 to 4 weeks. However, 2 trials followed subjects for 12 weeks, and 1 trial followed subjects for $\geq$ 1 year.

The placebo effect from massaging medicine into the skin is well known, although a meta-analysis that included 14 placebo-controlled trials of topical NSAIDs demonstrated a 48% response with active treatment compared with 26% for placebo alone.[40] To control for this effect, many of the studies included in this review used sprays or droppers to administer topical medication, or explicitly asked subjects to refrain from massage when applying topical formulations. Other nonpharmacologic placebo treatments may have also masked active treatment effects, and this was likely particularly pertinent in the acute-treatment trials. In the study by Akermark and Forsskåhl,[24] for example, subjects were allowed supplementary treatments, such as heating pads and stretching regimens, and this was likely to enhance the benefit of placebo while masking the effect of active treatment.

This review has a number of limitations. Several trials involved small numbers of subjects, which is known to influence treatment and placebo effects.[51] Various preparations of NSAIDs, different treatment schedules, and varied outcome measures were used in studies conducted over several decades. A minority of studies were not randomized, blinded, or placebo controlled.

Conclusion

This review of all available comparative trials and meta-analyses demonstrated topical NSAIDs to be superior to placebo formulations and to have similar outcomes compared with oral NSAIDs for the treatment of both acute and chronic musculoskeletal injuries. Gastrointestinal side effects were higher in participants receiving oral NSAIDs, while local skin reactions were more likely in topically treated subjects. Topical NSAIDs treatments may be considered as comparable alternatives to oral NSAIDs regimens and are rarely associated with serious adverse events and GI reactions in particular. Minor local skin reactions may limit use of topical NSAIDs for a minority of users.

Conflict of Interest Statement

Stephen A. Klinge, MD, and Gregory A. Sawyer, MD, disclose no conflicts of interest.

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