Massey T, Derry S, et al. Topical NSAIDS for acute pain in adults. Cochrane Database of Systematic Reviews 2010, issue 2, article # CD007402.

Design: Meta-analysis of randomized clinical trials

Purpose of study: to estimate the effectiveness of topical NSAIDS for acute pain from musculoskeletal injuries

PICOS:

- Patient population: adults 16 years or older with acute pain of at least moderate intensity from sprains, strains, or sports injuries, generally having occurred within 24 to 48 hours

- Interventions: any topical NSAID which is applied at least once daily
    - Salicylates were excluded because they were not considered to be NSAIDS
- Comparisons: inert preparations such as an inert carrier of an NSAID; other active treatments (such as other topical NSAIDS) or oral NSAIDS were considered for comparison
- Outcomes: 'clinical success" defined as a 50% reduction in pain or other equivalent measure, such as a "very good" or "excellent" global assessment of treatment, ascertained close to seven days (minimum of three days) from start of treatment
    - Thus, clinical success was dichotomized into success/failure, and the "relative benefit" (RB) of success was the outcome used to pool data (that is, a RB of 2.0 means that the topical NSAID was twice as likely to have a clinical success than the control intervention
    - Numbers of adverse events and withdrawals were considered as secondary outcomes
    - Only patient-reported outcomes were considered; clinician assessment of success was not considered as an outcome
- Study types: double-blinded randomized clinical trials with at least 10 patients per treatment group

Study selection:

- Databases were MEDLINE, EMBASE, the Cochrane Central Registry, and the Oxford Pain Relief Database, searched through December 2009
- Two authors independently assessed article for meeting inclusion criteria and for quality, with emphasis on risk of bias with respect to random sequence generation, allocation concealment, and blinding of all outcomes
    - Trial validity was assessed using a 16 point scale (The Oxford Pain Validity Scale, OPVS, reported in Smith 2000) which considers blinding, size of trial groups, having an outcome which is pre-defined before data are available, baseline pain and internal sensitivity (enough pain at baseline to allow for a

treatment effect to be detected), data analysis, statistical testing, and accounting for dropouts
    - A score of 8 or less was considered low quality, and a score of 9 or more was considered adequate
- The authors planned a sensitivity analysis which would compare studies of high and low quality, if there were sufficient numbers of studies of different levels of quality to permit the comparison to be made

Results:

- A total of 47 studies were included in the review, 31 comparing topical NSAID with placebo, 12 comparing a topical NSAID with an active treatment, and 4 having both active and placebo treatment arms for comparison with topical NSAIDS
- All studies were characterized as randomized and double blind
    - 42 studies scored 9 points or higher on the OPVS, and 7 scored 8 points or fewer
- When all topical NSAIDS were compared to placebo (31 studies, 1822 patients treated with NSAID and 1633 with placebo) , topical NSAIDS were more successful than placebo
    - The RB for success was 1.53 with 95% confidence intervals from 1.43 to 1.63); 65% of NSAID patients were successful versus 43% of placebo patients
        - For diclofenac, 3 studies with 627 patients showed a RB of 2.1 in favor of diclofenac (95% CI from 1.7 to 2.6)
        - For ibuprofen, the RB from 5 studies with 436 patients was 1.6 (95% CI from 1.3 to 2.0)
        - For ketoprofen, the RB from 7 studies with 683 patients was 1.6 (95% CI from 1.4 to 1.8)
        - For piroxicam, the RB from 3 studies with 504 patients was 1.5 (95% CI from 1.3 to 1.7)
        - For indomethacin, the RB from 2 studies with 295 patients was 1.3 (95% CI from 1.03 to 1.6)
        - For benzydamine, the RB from 3 studies with 193 patients was 1.2 (95% CI from 0.96 to 1.4), which is statistically not better than placebo
- When topical NSAIDS were compared with oral NSAIDS, there were insufficient data for meta-analysis because no two studies made the same comparison, but ibuprofen foam had a success rate of 24/50 patients (48%), while ibuprofen tablets had a success rate of 30/50 (60%); the two success rates were statistically equal
- Similarly, topical NSAIDS with different formulations of the same drug had insufficient data for analysis

- For the comparison of different topical NSAIDS, there were sufficient data only for the comparison of piroxicam versus indomethacin, where the RB in favor of piroxicam was 1.2 with a 95% CI from 1.1 to 1.4
    - In addition, there were significantly fewer adverse events with topical piroxicam (2.1%) than with indomethacin (10%)
- For topical NSAIDS versus oral NSAIDS, no serious adverse events were reported in either arm of any of the included studies
- For topical NSAIDS versus oral NSAIDS, no attempt was made to analyze the comparison of systemic adverse events of a less serious nature
- For local skin reactions, topical NSAIDS and placebo gels were no different in the rates of these events, which were described as mild and transient

Authors' conclusions:

- Topical NSAIDS can provide good pain relief in acute settings such as sprains, strains, and overuse injuries, with little difference in efficacy between topical diclofenac, ibuprofen, ketoprofen, and piroxicam, but indomethacin is less effective and benzydamine is no better than placebo
- Topical NSAIDS are no associated with an increase in skin reactions compared to placebo, and do not cause systemic (gastrointestinal) events commonly seen with oral NSAIDS, making them useful for patients who cannot tolerate oral administration of NSAIDS

Comments:

- There is only a single paragraph comparing systemic adverse events between topical and oral NSAIDS, which makes no attempt to pool data from comparative studies and simply reports that there were 16 adverse events among 797 patients (2%), but 11 events among 134 patients taking ibuprofen tablets (8%)
- Most studies were of minor muscle or joint trauma, which includes many lower extremity injuries such as sprains, even if the effect of topical NSAIDS on lower extremity acute injuries cannot be directly estimated
- Because the relative safety of topical NSAIDS is one of the most important factors affecting the decision to prescribe them over oral medication, this represents a regrettable lack of information concerning the main consideration in treatment decisions, and the difficulty arises from the lack of reporting in the included articles rather from a lack of effort by the authors
    - The summary of adverse events is in Table 2, which has a column for systemic adverse events and a separate column for serious adverse events
    - The majority of studies reported no systemic adverse events, and no study reports serious adverse events
    - Three studies made direct comparisons of topical versus oral NSAIDS

        - One study is useless because it reports data for events but not for patients
        - A second study reports 6 adverse events but declares none of them to be related to treatment and does not say whether they were with oral or topical NSAIDS
        - The third study compares felbinac foam with ibuprofen tablets, and reports 14/127 GI events for felbinac foam, asserting that these events were mild and not definitely drug related, while there were 11/134 GI events with ibuprofen, all of them definitely drug related
        - The journal for this third study is not indexed in PubMed but is indexed in EMBASE, where the abstract only asserts that both treatments were well tolerated; the study is for low back pain and not for lower extremity conditions
    - The rates of systemic events for topical NSAIDS, 16 adverse events among 797 patients, was apparently compiled from all included studies in which a topical agent was used, whether or not an oral NSAID was the control intervention
- Thus, the conclusion of the authors that topical NSAIDS can safely be used in patients not able to tolerate oral NSAIDS is not derived from direct comparisons, and is weakened by this lack of adequate reporting of adverse events in the three studies which did make that direct comparison
    - Unlike the comparison of topical NSAIDS with placebo, for which the cumulative evidence is strong, the evidence for GI events is better characterized as “some”

Assessment: An adequate meta-analysis which supports strong evidence that topical NSAIDS are more effective than placebo vehicles such as gels or creams in the setting of acute musculoskeletal injuries, and for some evidence that topical NSAIDS are associated with fewer systemic adverse events than oral NSAIDS

Reference:

Smith LA, Oldman AD, McQuay HJ, Moore RA. Teasing apart quality and validity in systematic reviews: an example from acupuncture trials in chronic neck and back pain. Pain 2000;86(1-2):119–32.