The current *JAMA* has a segment entitled "Clinical Evidence" Synopsis [1]," which this month deals with the intriguing issue of gauging the efficacy of nonsteroidal pain-relieving medications applied topically (as a gel applied to the skin overlying the pain source), as opposed to taking the same medication in pill form.


Their mission is simply stated. Are topical nonsteroidal anti-inflammatory drugs (NSAIDs) associated with reduced pain intensity in acute musculoskeletal conditions, but without increased adverse events? Their somewhat surprising conclusion: When treating musculoskeletal conditions such as sprains, strains, and contusions, topical NSAIDs are associated with greater pain relief, but are not associated with an increase in adverse events compared with placebo.

But how did they arrive at this conclusion? To figure that out, we must delve into the background work these authors have done over recent years that supplied the evidence for their conclusion. The trail was not hard to find.

Last year, in a *Cochrane Review* [2] publication [2], these same authors published a large meta-analysis assessing those high-quality studies which addressed topical treatments vs. inactive carrier-only (placebo) treatments for conditions involving acute musculoskeletal pain. The underlying causes ranged from conditions such as a sprained ankle or a muscle pull. These usually get better over two or three weeks without treatment, but can be very painful while they last.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are applied to unbroken skin over or near the painful area. Topical NSAIDs penetrate the skin, enter tissues or joints, and reduce processes causing pain in the tissue. Drug levels in the blood with topical NSAIDs are very much lower than
with the same drug taken by mouth, hopefully minimizing the risk of harmful effects.

The authors searched medical databases for clinical trials comparing topical NSAIDs with placebo (creams or gels that do not contain a medicine) or other medicines in adults aged 16 years or older with musculoskeletal pain (typically sports injuries). They identified 14 new studies to add to the 47 studies they had included in their earlier review. The 61 included studies, involving 8,386 participants, were generally of high-quality. The selected studies tested a number of different topical drugs, mostly against a topical placebo (carrier without the NSAID), with application at least once a day. Those deemed effective produced "good" pain reduction at least 50 percent less pain by seven days after treatment started. (At later times, most people are expected to get better even without treatment.)

The drugs and formulations evaluated included gel formulations of diclofenac and ketoprofen, which were among the most effective, along with ibuprofen gel and diclofenac plaster. For diclofenac and ketoprofen gels, about three-quarters of those with a painful strain, sprain, or muscle pull had much reduced pain after seven days, compared with only one-fourth with placebo. Other NSAIDs and formulations were better than placebo, but not by as much. Because both topical NSAIDs and topical placebo are rubbed into the skin in these studies, we know that any effect is not just from rubbing.

About one in 20 people experienced a mild and short-lived side effect like redness at the application site. This was the same for topical NSAID and topical placebo (high quality data). Side effects like a stomach upset or feeling sick were uncommon, with no difference between topical NSAID and topical placebo (high quality data). There were no serious side effects.

The bottom line is this: topical NSAIDs provided good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, similar to that provided by oral NSAIDs. Gel formulations of diclofenac (as Emugel®), ibuprofen, and ketoprofen, and some diclofenac patches, provided the best effects.

Adverse events were usually minimal. Getting satisfactory pain relief from topical drugs eliminates (or markedly reduces) the most feared side effect of these drugs: GI bleeding, which was not seen in the evaluated studies. Local reactions and even possibly allergic reactions cannot be eliminated by this route, but on the whole, this is very important information, for ER doctors and primary care doctors as well as orthopedists and sports medicine docs.
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