Radiology

(Still) Wondering If We Should Stop Giving Steroid Preps

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The evidence supporting corticosteroid prophylaxis (ie, "steroid prep") for the prevention of immediate hypersensitivity contrast material reactions is a complex mix. It consists of a cobbling of tangentially related research on now-outdated contrast materials, a single underpowered randomized trial on average-risk patients with inconclusive results, and inferential observational studies with dubious control groups (1–4). Despite this, it is in widespread use in multiple countries. How did we get here?

Steroid preps were popularized in the 1980s (1). At that time, contrast material reactions were common, and commonly dangerous (1,2), so there was a strong need to mitigate their frequency and severity. In 1987, Lasser et al (1) demonstrated in a multicenter randomized trial of 6763 average-risk patients that an oral, two-dose (32 mg/dose), 12-hour regimen of methylprednisolone was effective at preventing reactions compared with a placebo (reactions necessitating therapy: 1% vs 2%, $P = .008$; all reactions: 6% vs 9%, $P < .001$) (1). These data established the foundation for using prophylaxis to prevent contrast material reactions.

However, there were problems in applying those results to modern practice. Principally, the 1987 Lasser et al trial (1) evaluated patients receiving high-osmolality iodinated contrast materials—contrast materials no longer used for intravascular applications and that which have a much higher reaction rate than the low- and iso-osmolality iodinated contrast materials used today (2). Lasser et al (1) also studied patients at average risk for a contrast material reaction, not patients with risk factors (2). Finally, the reaction classification used in their study conflated physiologic and hypersensitivity reactions and did not conform to modern stratification schemas of reaction type and severity (1,2).

There is also relevant historical context. At the time, low-osmolality iodinated contrast materials were expensive. Lasser et al (1) offered corticosteroid prophylaxis "as a reasonable alternative to intravenous nonionic (low-osmolality) medium, without loss of safety." Their study design was repeated in 1994 with low-osmolality materials, but the trial was insufficiently powered, and statistically significant reductions in moderate or severe reactions were not demonstrated (3). Therefore, despite widespread use of prophylaxis in some countries at present, no strong evidence shows that it is effective in preventing important reactions to modern contrast materials or in patients with a previous contrast material reaction.

The weak evidence supporting corticosteroid prophylaxis (4), and its potential risks (2,5), have led to lukewarm and negative recommendations from major societies (2,6,7). The current American College of Radiology guidelines state: "The utility of premedication in high-risk patients is uncertain…(but) premedication may be considered in (some) settings and scenarios (ie, prior immediate hypersensitivity or unknown-type reaction to the same class of contrast medium)" (2). The current European Society of Urogenital Radiology guidelines state: "Premedication is not recommended because there is not good evidence of its effectiveness" (6). The 2020 Joint Task Force on Practice Parameters for Allergy and Immunology state: "We suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast hypersensitivity reactions (conditional recommendation, certainty rating of evidence: very low)," and "Higher certainty evidence is needed to better inform practice" (7). In short, the evidence supporting prophylaxis in modern care pathways is weak, the effect size of prophylaxis is small and incomplete, prophylaxis may cause more harm than good in certain populations, and several major professional societies believe that in the absence of better evidence of efficacy, corticosteroid prophylaxis may not be worth doing (1–7).

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See also the article by McDonald et al in this issue.

It is in this meta-environment that McDonald et al (8) conducted a retrospective cohort study of 1973 patients with a previous immediate hypersensitivity reaction to iodinated contrast materials (ie, patients at high-risk for a contrast material reaction) who received 4360 subsequent contrast-enhanced CT examinations. Chart review determined the intervention (prophylaxis with 12- and 2-hour oral methylprednisolone [32 mg/dose, identical to the Lasser et al {1} protocol {4}] and/or switching the contrast material, or neither) and the outcome (repeat immediate hypersensitivity contrast material reaction or no reaction). The authors found that premedication was not effective in preventing a repeat reaction in patients receiving the same contrast material as the initial reaction (26% [44 of 172 patients with prophylaxis, ie, "breakthrough reactions"] vs 25% [73 of 298 patients without prophylaxis], odds ratio, 1.00; $P = .99$) but changing the contrast material was strongly effective in preventing a repeat reaction (odds ratio, 0.12 [95% CI: 0.04, 0.36] to 0.14 [95% CI: 0.06, 0.33]; $P < .001$). These results have two powerful messages—changing the culprit contrast material, if feasible, likely is strongly protective against a repeat hypersensitivity contrast material reaction, and corticosteroid prophylaxis with standard-of-care dosing does not seem to be effective in patients at high-risk of developing a reaction. In other words, these results have the potential to change the standard of care.

Others have shown that changing the culprit contrast material prevents hypersensitivity contrast material reactions, and the benefits of corticosteroid prophylaxis in patients at high-risk for a contrast material reaction might be minor or negligible (eg, see reference 9). However, in general, such studies have used smaller sample sizes (8,9) and have tested nonstandard prophylaxis regimens that have limited generalizability to the standard of care. The study by McDonald et al (8) represents the most substantive evidence to date refuting standard-of-care corticosteroid prophylaxis and supporting changing the culprit contrast material in patients with a prior hypersensitivity contrast reaction. Their results also suggest that if the culprit contrast material is unknown or an alternative contrast material is not available, then withholding prophylaxis is not more harmful than giving it. However, the study was not powered for noninferiority, and the direct and indirect risks of prophylaxis were not assessed (8).

Does this mean we can stop using steroid preps? Like all questions in medicine, it is a risk-benefit assessment followed by a value judgment about the strength of evidence. Before the study by McDonald et al (8), it had been estimated that in the best-case scenario, the number needed to treat to prevent a contrast material reaction in a high-risk patient was approximately 570 for a severe reaction and approximately 50 000 for a lethal reaction (4,5,10). Furthermore, it had been shown that in vulnerable patient populations (eg, inpatients), long oral corticosteroid regimens probably cause more harm than good because of prolonged hospitalization and its related costs and morbidity (4,5). If corticosteroid prophylaxis for the prevention of hypersensitivity contrast material reactions was still considered appropriate before the work by McDonald et al (8), then changing practice now requires an assessment of the new strength of evidence. Major limitations of the study by McDonald et al (8) include the retrospective sample contributing a risk of selection bias, single-center design, and lack of randomization (8). Some of these biases could obscure a protective effect of prophylaxis if, for example, patients at higher risk of a contrast material reaction were administered prophylaxis and patients at lower risk of a contrast material reaction were not. However, when squared against the limitations in the data supporting prophylaxis, one can, in our opinion, readily make an argument that the evidence has tipped in favor of discontinuing the practice.

So where does this leave us? Here is our take. The American College of Radiology should strongly consider updating the Manual on Contrast Media (2) to align with other professional organizations and should state, "Evidence supporting corticosteroid prophylaxis is limited. Routine use of prophylaxis with corticosteroids and/or antihistamines for the prevention of hypersensitivity contrast material reactions is not indicated for low- or iso-osmolality iodinated contrast materials, even in patients with a previous hypersensitivity contrast material reaction. In patients with a previous hypersensitivity contrast material reaction, avoid giving the same material. In patients with a previous severe hypersensitivity contrast material reaction, refer to an allergist for testing before administering the same class of contrast materials." These changes would have a broad and powerful effect on patient care and would be supported by evidence. We also believe there is sufficient equipoise to warrant a prospective multicenter trial that modernizes the efforts undertaken by Lasser et al in the 1980s (1) and 1990s (3). Such a trial should include a large, adequately powered sample of patients with a previous hypersensitivity reaction to iodinated contrast materials who are randomized to receive corticosteroid prophylaxis versus a placebo. We believe there is ethical justification for such a trial given the known benefits and risks of prophylaxis. If we wish to continue (or restart) using corticosteroid prophylaxis for the prevention of hypersensitivity contrast material reactions, then we first need evidence it actually works.

In conclusion, McDonald et al (8) have furthered the evidence against corticosteroid prophylaxis and for changing the culprit contrast material in patients with a previous hypersensitivity contrast material reaction. It is time to update our guidelines and to move forward with a definitive trial.

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