Anesthesiology 2007; 107:358–9

Preoperative Cyclooxygenase-2 Inhibitor Treatment Reduces the Incidence of Heterotopic Ossification after Hip Arthroplasty: Six-month Follow-up

To the Editor:—In a recent article in ANESTHESIOLOGY,[1] we described the up-regulation of prostaglandin E_2 (PGE_2) in hip drain fluid at 24 h after total hip arthroplasty (THA), and the reduction of this PGE_2 by preoperative cyclooxygenase-2 (COX-2) inhibitor administration. We have continued follow up on these patients to determine whether there was any relation between the preoperative COX-2 inhibitor treatment and the long-term development of heterotopic ossification (HO), based on radiologic evaluation.

Heterotopic ossification is the formation of bone in the muscles and connective tissue surrounding joints. HO is not only recognized as one of the common complications of THA, but has also been reported after other surgical procedures. Even with long-term postoperative nonsteroidal antiinflammatory drug or COX-2 inhibitor treatment, the incidence of HO after THA is 14–18%.[2] In an older study, the incidence of HO in untreated patients was 65%,[3] so intervention of some form is desirable. The formation of this ectopic bone can be painful, and patients may require further complex surgery in severe HO.[4]

The usefulness of nonsteroidal antiinflammatory drugs and COX-2 inhibitors in HO prophylaxis suggests that prostaglandins may play a critical role. In a recently published report using a rabbit model of HO, increases in PGE_2 and PGF_2-α at the local tissue site in the first 24–48 h were associated with the later development of HO.[5] Our follow-up clinical study was undertaken to test the hypothesis that early intervention with COX-2 inhibitors can prevent HO, and that locally released prostaglandin from surgical trauma is related to the occurrence of HO at 6 months postoperatively.

After institutional review board approval from Rush University Medical Center (Chicago, Illinois) and written informed consent, 23 osteoarthritis patients undergoing primary THA who were randomly assigned to three groups were analyzed (same group of patients in the previous publication[1]): oral rofecoxib, 50 mg each day for 4 days before surgery and on the morning of surgery (5-day dose group); oral placebo each day for 4 days before surgery and 50 mg rofecoxib on the morning of surgery (single-dose group); and oral placebo each day for 4 days before surgery and on the morning of surgery (placebo group). A standardized surgical technique was performed using noncemented hip arthroplasty. Before closing the surgical incision, a hip drain catheter was placed in the wound, and exudates were collected in a reservoir. At 23 h from the start of surgery, the hip drain reservoir was emptied, and the exudates were collected over the next 60 min for later PGE_2 analysis. Radiographs at 6 months after surgery were reviewed by an investigator, blinded to the group allocation, to grade HO according to Brooker's criteria (grades 0–4).[6]

Patient demographics (age, weight, height, race, sex) did not differ among the three groups.[1] There was a difference among the three treatment groups in the presence (Brooker grade $>$ 0) or absence (Brooker grade 0) of HO ($P = 0.0336$, Mantel-Haenszel chi-square test). The incidence of HO was 6 in 9 in the placebo group, 2 in 7 in the single-dose group, and 1 in 7 in the 5-day dose group. Only one patient, in the placebo group, had severe HO (Brooker grade 3). Patients with 5-day rofecoxib dosing had a lower incidence of HO than patients who received placebo ($P = 0.0361$). The surgical site PGE_2 concentration in patients who later developed HO (27,936 ± 4,882 pg/ml, mean ± SEM) was greater than in patients with no observable HO (13,242 ± 3,635 pg/ml) (fig. 1; $P = 0.0275$, Mann–Whitney test).

Our analysis demonstrates that preoperative COX-2 inhibitor treatment reduces the incidence of HO. Although long-term postoperative nonsteroidal antiinflammatory drug or COX-2 inhibitor administration, or postoperative irradiation, are also effective in reducing HO,[2,3] short-term preemptive treatment with a COX-2 inhibitor seems preferable. A single preoperative radiotherapy dose has been shown to be as effective as postoperative radiation in preventing HO, leading to the conclusion that the beneficial effects of prophylaxis for HO lie in the immediate perioperative period.[7] Similar to the recent animal study on HO,[5] our preliminary results suggest that early increases in PGE_2 precede the later development of heterotopic bone formation.

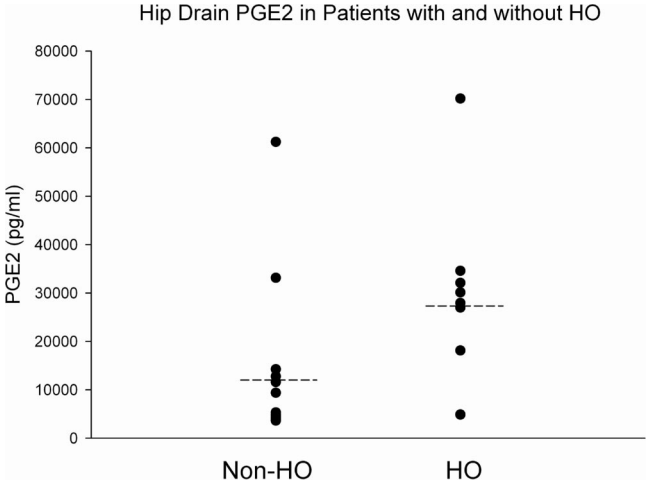

Fig. 1. Tissue prostaglandin E_2 (PGE_2) concentration at 24 h after total hip arthroplasty in patients with heterotopic ossification (HO) or without (non-HO) at 6-month radiologic follow-up. *Dotted lines* represent mean value for each group.

The presence of low-grade HO (1 and 2) after THA may not require interventional treatment; however, they were included in this analysis because the sample size was small and the main hypothesis was to determine whether preoperative COX-2 inhibitor treatment affects the development of HO. Although only severe Brooker HO grades are of clinical importance, the incidence of HO is often the primary variable in research studies. Given the current literature on increased cardiovascular risks of patients taking long-term COX-2 and nonsteroidal antiinflammatory drugs,[8] it might be beneficial that patients undergoing THA get a single high-dose preoperative treatment with these agents for prevention of HO. Although future studies are contingent on safety issues with the whole class of COX-2 inhibitor drugs, the consequences of ectopic bone formation after THA may still warrant a prospective trial of a single large dose of preoperative COX-2 inhibitor in a larger number of patients.

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(Accepted for publication March 12, 2007).

Anesthesiology 2007; 107:359

Paradoxical Vocal Cord Movement: A Unique Case of Occurrence and Treatment

To the Editor:—Paradoxical vocal cord movement (PVCM) is a well-described condition that involves adduction of the vocal cords on inspiration, which in turn causes stridor and respiratory distress.[1–3] We report a unique case of severe PVCM wherein a patient had severe PVCM immediately after treatment of the disease with botulinum toxin type A (Botox) injection of the vocal cords; the PVCM was immediately and dramatically successfully treated with a small dose of intravenous sedation without any further life-threatening symptoms.

A 30-yr-old woman was scheduled to undergo direct laryngoscopy and Botox injection to the vocal cords for PVCM. Four weeks and 1 week before the procedure, she had been tracheally intubated, mechanically ventilated for 1–2 days, and then extubated. Just before the first tracheal intubation, PVCM was diagnosed fiberoptically. The patient also had a medical history notable for anorexia, bulimia, and symptomatic gastroesophageal reflux disease. After the uncomplicated induction of general anesthesia, paralysis with succinylcholine, and tracheal intubation, the true vocal cords were injected with 2.5 U Botox in each thyroarytenoid space. After the 20-min procedure, the patient was fully awake, extubation criteria were met, and the patient was extubated. She was transported to the postanesthesia care unit receiving oxygen by facemask. During transport to the postanesthesia care unit, she reported chest tightness, began having audible stridor, and reported that she was unable to breathe as she forcibly removed her oxygen mask. She had no pain but continued to report chest tightness and inability to breathe and now had loud, disturbing inspiratory stridor. She was given 2 mg intravenous midazolam, which resulted in immediate resolution of all of her impressive and concerning symptoms. She remained well oxygenated on room air, remained stable, and was void of stridor until her discharge to home 2 days later.

In summary, we present a unique case of PVCM that was treated with Botox, which was quickly followed by an episode of severe stridor, which immediately resolved with intravenous midazolam. The dramatic response to a small amount of sedation highlights the importance of underlying psychogenic responses in some of these patients. The case report highlights the delay that may occur in the action of Botox and severe symptoms that may occur immediately after the procedure.

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(Accepted for publication March 20, 2007.)