Perioperative Analgesia: What Do We Still Know?

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Current clinical practices designed to minimize pain in the perioperative period should be based on scientific evidence from the peer-reviewed medical literature.[1] The recent and unprecedented retraction of 21 peer-reviewed articles and abstracts published by Dr. Scott S. Reuben, a leading investigator in the perioperative use of nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, raises important questions as to the potential adverse impact of Dr. Reuben's fraudulent work on the practice of acute (perioperative) pain management. The purpose of this editorial is to provide a brief overview of the status of the field, distinguishing our understandings that remain fully supported from those that are no longer supported by the unimpeached literature.

The classical NSAIDs and the newer COX-2 drugs have been reported to provide effective postoperative analgesia and opioid-sparing effects after a wide variety of both in- and outpatient surgical procedures by numerous investigative groups around the world. In one of their retracted articles (Table 1, Ref. 1), Reuben et al. reported that the COX-2-specific NSAIDs celecoxib and rofecoxib both reduced pain scores and produced opioid-sparing effects after orthopedic surgery. These investigators also reported in a retracted article (Table 1, Ref. 2) that the administration of rofecoxib was not associated with a significant increase in the incidence of perioperative bleeding in patients undergoing total knee arthroplasty (TKA), supporting their recommendation that the COX-2 inhibitors did not need to be discontinued before elective surgery. Two other retracted articles studied the effects of rofecoxib and celecoxib when administered for perioperative analgesia in patients undergoing knee reconstruction procedures and similarly noted reductions in pain scores, opioid consumption, and side effects (Table 1, Refs. 3 and 4).

In another recently published and now retracted article (Table 1, Ref. 5), these investigators reported that perioperative use of celecoxib reduced postoperative pain, opioid consumption, opioid-related adverse effects, and was associated with long-term benefits, including improved knee function and less time to achieve effective range of motion after TKA. These findings confirmed an earlier study by Buvanendran et al.,[2] who reported that perioperative use of rofecoxib as part of a multimodal analgesic technique reduced opioid consumption, pain, vomiting, and sleep disturbance, with improved knee range of motion after TKA. Of interest, Ma et al.[3] found that, although perioperative rofecoxib was effective in improving postoperative pain management, as well as the speed and quality of early recovery after outpatient inguinal herniorraphy, it failed to accelerate the resumption of normal activities of daily living in the postdischarge period. However, a more recent study by White et al.[4] reported that short-term administration of celecoxib after outpatient laparoscopic surgery decreased postoperative pain and the need for opioid-containing analgesic medication, leading to an improved quality of recovery (including recovery of bowel function and resumption of physical activities).

Several controversial topics related to perioperative NSAID use were investigated by Dr. Reuben and his colleagues during the last decade. Although animal data suggested that the preemptive administration of

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Table 1. Partial List of Retracted Manuscripts

1. Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000;91:1221–5
2. Reuben SS, Fingeroth R, Krushell R, Maciolek H. Evaluation of the safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. J Arthroplasty 2002;17:26–31
3. Reuben SS, Gutta SB, Sklar J, Maciolek H. Effect of initiating a multimodal analgesic regimen upon patient outcomes after anterior cruciate ligament reconstruction for same-day surgery: a 1200-patient case series. Acute Pain 2004;6:87–93
4. Reuben SS, Ekman EF, Charron D. Evaluating the analgesic efficacy of administering celecoxib as a component of multimodal analgesia for outpatient anterior cruciate ligament reconstruction surgery. Anesth Analg 2007;105:222–7
5. Reuben SS, Buvenandran A, Katz B, Kroin JS. A prospective randomized trial on the role of perioperative celecoxib administration for total knee arthroplasty: improving clinical outcomes. Anesth Analg 2008;106:1258–64
6. Reuben SS, Ekman EF. The effect of cyclooxygenase-2 inhibition on analgesia and spinal fusion. J Bone Joint Surg Am 2005;87:536–42
7. Reuben SS, Reuben JP. Brachial plexus anesthesia with verapamil and/or morphine. Anesth Analg 2000;91:379–83
8. Reuben SS, Vieira P, Faruqui S, Verghis A, Kilaru P, Maciolek H. Local administration of morphine to bone following spinal fusion surgery. Anesthesiology 2001;95:390–4
9. Reuben SS, Steinberg RB, Maciolek H, Manikantan P. An evaluation of the analgesic efficacy of intravenous regional anesthesia with lidocaine and ketorolac using a forearm versus upper arm tourniquet. Anesth Analg 2002;95:457–60
10. Reuben SS, Rosenthal EA, Steinberg RB, Faruqi S, Kilaru PR. Surgery on the affected upper extremity of patients with a history of complex regional pain syndrome: the use of intravenous regional anesthesia with clonidine. J Clin Anesth 2004;16:517–22
11. Reuben SS, Pristas R, Dixon D, Faruqi S, Madabhushi L, Wenner S. The incidence of complex regional pain syndrome after fasciectomy for Dupuytren's contracture: a prospective observational study of four anesthetic techniques. Anesth Analg 2006;102:499–503
12. Reuben SS, Connelly NR. Postarthroscopic meniscus repair analgesia with intraarticular ketorolac or morphine. Anesth Analg 1996;82:1036–9
13. Reuben SS, Ekman EF. The effect of initiating a preventive multimodal analgesic regimen on long-term patient outcomes for outpatient anterior cruciate ligament reconstruction surgery. Anesth Analg 2007;105:228–32
14. Reuben SS, Ekman EF, Raghunathan K, Steinberg RB, Blinder JL, Adesioye J. The effect of cyclooxygenase-2 inhibition on acute and chronic donor-site pain after spinal-fusion surgery. Reg Anesth Pain Med 2006;31:6–13
15. Reuben SS, Connelly NR, Maciolek H. Postoperative analgesia with controlled-release oxycodone for outpatient anterior cruciate ligament surgery. Anesth Analg 1999;88:1286–91
16. Reuben SS, Makari-Judson G, Lurie SD. Evaluation of efficacy of the perioperative administration of venlafaxine XR in the prevention of postmastectomy pain syndrome. J Pain Symptom Manage 2004;27:133–9
17. Reuben SS, Buvanendran A, Kroin JS, Steinberg RB. Postoperative modulation of central nervous system prostaglandin E2 by cyclooxygenase inhibitors after vascular surgery. Anesthesiology 2006;104:411–16
18. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery. Anesth Analg 2006;103:1271–7

analgesic drugs may reduce postoperative analgesic requirements and minimize the development of hypersensitivity to a greater extent compared with preventive administration of the same drug,[5] the clinical evidence supporting this claim has been questioned by several investigative groups.[6–9] Reuben and his colleagues have consistently reported that NSAIDs produce a "preemptive" effect when they were administered before versus after the surgical incision. In an article that was not on the list of articles which were retracted, Reuben et al.[10] reported that the administration of rofecoxib before arthroscopic knee surgery provides a longer duration of analgesia, less 24-h opioid use, and lower pain scores than administering the same dose of the drug after the completion of surgery. However, this is in disagreement with systematic reviews of pre- versus postsurgical preemptive administration of NSAIDs.[6–8] In a recent article in this journal,[9] celecoxib administered on the day of surgery and for 3 days postoperatively was reported to be effective in improving postoperative pain management, and the speed and quality of recovery after major plastic surgery. However, perioperative administration offered no advantages over simply giving the drug after surgery. These data clearly indicate the absence of any preemptive effects of the COX-2 antagonists.

Another controversial area of research relates to the potential adverse effect of NSAIDs and COX-2 inhibitors on bone healing. In one of the retracted articles, Reuben and Ekman (Table 1, Ref. 6) reported that the perioperative (short term) administration of celecoxib had no apparent effect on the rate of nonunion at the time of the 1-yr follow-up evaluation. In more recent studies published by Pradhan et al.[11] and Sucato et al.[12] involving patients undergoing spinal surgery, use of the nonspecific NSAID, ketorolac, was not found to alter "ultimate bone fusion rates" or the incidence of pseudoarthrosis, respectively. However, based on recent studies in rodent models,[13] further clinical studies in this area are required with the COX-2-specific analgesics.[14]

Reuben and colleagues have also investigated several novel routes of administration of NSAIDs and other drugs for postoperative analgesia (e.g., intraarticular, local, and regional analgesia). For example, in one of the Reuben's retracted articles, the addition of verapamil or morphine to brachial plexus block with lidocaine was reported to prolong the duration of sensory anesthesia (Table 1, Ref. 7). In another of the

retracted articles, low-dose morphine applied to the harvest graft site was reported to reduce local pain, morphine use, and chronic donor site pain after cervical spine fusion surgery (Table 1, Ref. 8). These results should be seriously questioned in light of the limited efficacy reported by other investigative groups with peripheral opioid and non-opioid analgesic administration.[15–17]

A series of retracted articles involved the administration of various adjuvants to the local anesthetic for IV regional anesthesia (IVRA) (Table 1, Refs. 9–11). For example, forearm tourniquet IVRA with lidocaine and ketorolac provided for both a longer duration of sensory block and more prolonged postoperative analgesia compared with upper arm IVRA (Table 1, Ref. 9). Reuben et al. (Table 1, Ref. 10) reported that intraoperative IVRA with lidocaine and adjunctive clonidine in patients with a history of complex regional pain syndrome significantly reduced the recurrence rate of this disease process. A follow-up study which was also retracted reported that an axillary block or IVRA with the addition of clonidine offered a significant advantage for decreasing the incidence of complex regional pain syndrome compared with either IVRA with lidocaine alone or general anesthesia for patients undergoing Dupuytren's surgery (Table 1, Ref. 11). Reuben and Connelly (Table 1, Ref. 12) also concluded in another one of their retracted articles that the use of both intraarticular ketorolac and intraarticular morphine improved the comfort in patients undergoing arthroscopic meniscus repair. The drug combination was reported to offer no advantage over either drug alone. When it was published, the results were surprising because these two analgesics have totally different mechanisms for producing their analgesic actions, and at least three systematic reviews had suggested that these drugs possess limited, if any, local analgesic effects.[15–17] Based on this set of retractions, all of these findings must now be considered unsubstantiated.

As described in two recent nonretracted review articles, a major focus of Dr. Reuben's work has been in the area of preventing chronic pain by implementing perioperative preemptive approaches to pain management with NSAIDs and COX-2 inhibitors.[18,19] In a retracted article by Reuben and Ekman (Table 1, Ref. 13), the perioperative administration of celecoxib as a component of a preventive multimodal analgesic technique for anterior cruciate ligament reconstruction was reported to reduce long-term patellofemoral complications and increased the likelihood of returning to a preinjury level of activity, a potentially important clinical outcome. The administration of celecoxib for the first 5 days after spinal-fusion surgery also resulted in improved analgesia and a reduction in chronic donor-site pain at 1 yr after surgery (Table 1, Ref. 14). Analogous to a previously mentioned retracted article (Table 1, Ref. 5), the nonretracted review article by Reuben and Buvanendran[18] described the prevention of chronic pain after orthopedic surgery with preventive multimodal analgesic techniques. Similarly, in a review article on the prevention of chronic pain after thoracic surgery that was not retracted, Reuben and Yalavarthy [20] state that "it is necessary to administer analgesics pre-, intra- and postoperatively" to minimize the development of chronic pain after major cardiothoracic procedures. Although these findings at first glance seem totally reasonable, the role of perioperative pain management in preventing chronic pain remains unproven.[21,22] Of interest, a recent study by Andersen et al.[23] found a surprisingly high incidence of chronic pain after major orthopedic surgery, despite the implementation of an aggressive multimodal analgesic regimen during the perioperative period.

It seems reasonable to ask whether Dr. Reuben published any negative studies involving investigational or recently approved analgesic drugs. Most of the retracted articles involved a new (or novel) analgesic drug or route of administration, and the findings reported were uniformly "favorable" to the new drug or technique. For example, one retracted article describing a new controlled-release formulation of oxycodone in patients undergoing anterior cruciate ligament repair on an ambulatory basis was reported to provide significant analgesic benefit and a decreasing of side effects compared with either fixed-dose or as-needed oxycodone regimens (Table 1, Ref. 15). In another retracted study, the perioperative administration of venlafaxine beginning the night before surgery significantly reduced the incidence of postmastectomy pain syndrome after breast cancer surgery (Table 1, Ref. 16). In yet another retracted article, Reuben et al. (Table 1, Ref. 17) reported that cerebrospinal fluid prostaglandin E2 levels were elevated in patients after lower extremity vascular surgery and postsurgical administration of the investigational COX-2 inhibitor parecoxib reduced the cerebrospinal fluid prostaglandin E2 concentration and postoperative pain. Finally, Reuben et al. (Table 1, Ref. 18) reported in a retracted article that the perioperative administration of pregabalin (150 mg) was comparable with celecoxib in improving postoperative analgesia after spinal fusion surgery. However, other recent studies[24–26] have reported that preoperative doses of pregabalin (ranging from 100 to 300 mg) fail to reduce postoperative pain or the amount of opioid analgesic medication required after surgery.

In summary, it is unprecedented in our specialty to retract a large body research spanning nearly 15 yr of active investigation and publication. A cursory review of both the retracted and unimpeached literature would lead us to conclude that:

1. Postoperative administration of COX-2 inhibitors has consistently been demonstrated to have beneficial effects in improving analgesia, reducing opioid-related side effects, and improving

quality of patient recovery in the early and intermediate postoperative period. However, the potential for long-term clinical benefits remains to be confirmed by other investigative groups.
2. There is no longer unequivocal evidence supporting the preemptive effect of NSAIDs and COX-2 inhibitors.
3. The ultimate clinical effect of NSAIDs and the COX-2 inhibitors, in particular, on bone fusion, remains unclear and further investigative work is needed in this controversial area.
4. The ability of a multimodal preemptive analgesic regimen to prevent the development of chronic pain after major orthopedic surgery remains unproven.

Finally, the retraction of Dr. Reuben's articles compromise every meta-analysis, editorial, and systematic review of analgesic trials that included these fabricated findings[7,8,15–17,27,28] and every lecture and Continuing Medical Education course on perioperative analgesia that included these studies.[29] Clearly, it is time to "get back to the (hard!) work" of conducting clinical analgesic studies[1] to address important issues in perioperative pain management and patient outcomes.

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