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Clinical Practice

Are perioperative therapeutic doses of statins associated with postoperative pain and opioid consumption after hip surgery under spinal anaesthesia?

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Abstract

Background. The anti-inflammatory effects of statins have been suggested to relieve postoperative pain. This retrospective study tested the association between the perioperative routine use of statins in therapeutic doses, and opioid requirements and pain scores, after hip replacement surgery.

Methods. With IRB approval, data was obtained for adult patients who had elective hip replacement surgery under spinal anaesthesia at Cleveland Clinic between 2005 and 2015. Patients were compared using a joint hypothesis framework. We used the inverse probability of treatment weighting method to control for observed confounding factors (a total of 26).

Results. We included 611 statin users and 780 non-statin users. Pain score during the initial 72 h after surgery was 0.07 higher (95% CI: −0.02, 0.17) in statin users (noninferiority test in both directions $P<0.001$). The estimated ratio of geometric means in the cumulative i.v. morphine equivalent opioid consumption was 1.01 (95% CI: 0.93, 1.10) for statin *vs* non-statin users (noninferiority test $P=0.001$ in the hypothesized direction and<0.001 in the other direction) during the initial 72 h after surgery. The statin and non-statin patients were deemed equivalent on postoperative opioid consumption and pain score.

Conclusions. This is the first large retrospective clinical study that investigates the effects of statin use on postoperative pain and opioid consumption. We observed no difference between statin users and non-users during the initial 72 h after hip surgery. Our findings do not support the routine use of statins as part of an analgesic regimen.

Key words: analgesia; analgesics, opioid; hydroxymethylglutaryl-CoA reductase inhibitors; perioperative period; pain, postoperative

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Editor's key points

- Preclinical evidence reveals anti-inflammatory, anti-nociceptive effects for statins. This may have clinical relevance perioperatively.
- Using a large clinical database this study explored how regular statin use affects postoperative pain.
- Using inverse probability of treatment weighting, neither postoperative pain nor opioid consumption were affected by statin use.
- Further prospective study of dose, type of statin and duration of use is required.

Postoperative pain remains the most common concern in 60% of surgical patients, despite the improvement of analgesic techniques.[1] Inadequate postoperative analgesia results in higher morbidity, delayed recovery, increased hospital stay, and more patient dissatisfaction.[2 3] Furthermore, it leads to prolonged suffering, limited mobility and venous thrombosis, unanticipated readmissions, and increased risk of chronic pain.[3–5]

Statins are among the most prescribed drugs in the US and roughly 25 million individuals are statin users worldwide.[6] As a result, statins use is also common in surgical patients. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate, the rate limiting step in biosynthesis of cholesterol.[7] Statins have potent anti-inflammatory effects which are evident by significant decreases in CRP or circulating pro-inflammatory cytokine levels, increase in nitric oxide levels, and via other anti-inflammatory mechanisms.[8] This anti-inflammatory property of statins has been suggested to influence postoperative pain control.[9 10] This results from the fact that surgical incision releases inflammatory mediators which reduce the pain threshold at the site of injury and in surrounding uninjured tissue.[6 11 12] Consistent with these observations, experimental studies using different animal models of pain suggest statins have an analgesic effect on nociceptive pain, neuropathic pain, and arthritic pain.[6 13–19] Moreover, studies in rats have shown that statins may increase the effectiveness of opioids by reducing opioid-tolerance.[20 21]

Available clinical literature does not address the relationship between perioperative statins use and postoperative pain and opioid consumption. In addition, there is conflicting evidence regarding the prolonged use of statins and the effect it carries on pain and nociception, as there is emerging evidence which is inconsistent and does not yet support the use of statins as analgesic adjuvants. In fact, a recent publication did not observe any difference in pain scores of patients admitted for epidural steroid injection when stratified by statin use.[22] Statin-induced myopathy (SIM), statin neuropathy, elevated liver enzymes, rhabdomyolysis, impaired cardiac contractility, and new-onset autoimmune diseases are some of the loosely-defined and controversial effects of long-term statin use and are implicated in increased pain.[23 24] These effects seem to be associated with enhanced activity of caspases and pro-apoptotic factors and destruction of elements of the neuronal network in lieu of less available cholesterol for the proper functioning of neurones.[23 25 26]

Given the widespread use of statins, our goal was to determine whether or not statins were independently associated with decreased postoperative pain and opioid consumption. We chose hip replacement surgery under spinal anaesthesia to ensure continuous use of statins perioperatively and to reduce confounding effects of regional anaesthesia or intraoperative opioid use. Specifically, we tested the primary hypothesis that the perioperative use of statins in routine therapeutic doses is independently associated with decreased opioid requirements and pain scores during the initial 72 h after hip replacement surgery.

Methods

With Institutional Review Board (IRB) approval, this retrospective cohort analysis was based on all available adult patients (≥18 yr of age) who had elective hip replacement surgery (partial or total) under spinal anaesthesia at the Cleveland Clinic between 2005 and 2015. The requirement for written informed consent was waived by the IRB. Patients undergoing emergent surgery or receiving additional regional or epidural analgesia other than spinal anaesthesia were excluded from the study population. Data was obtained from the Cleveland Clinic Perioperative Health Documentation System. The registry contains all patients who had non-cardiac surgery since 2005 at the Cleveland Clinic main campus and integrates preoperative variables (patient characteristics, conditions, etc.), intraoperative variables (via our Anaesthesia Record Keeping System), and postoperative outcomes (by linking to the larger Cleveland Clinic billing data systems). The clinical routine is to record pain scores every 15 min in the post anaesthesia care unit and every four h on the ward, and we have included all available pain scores. The total opioid consumption was converted to i.v. morphine equivalents for analysis (Supplementary Appendix 1).[27] A "current statin user" was defined as a patient with an active statin prescription within 30 days before surgery. The electronic database at our institution collects information on active medication prescriptions typically within 30 days. This database is updated at the preoperative visit which occurs within 2 weeks before the date of surgery. Routine management of patients on statin therapy includes continuation of the statin until the day of surgery and the treatment is re-established as soon as the patient can tolerate food. At our institution, as a standard of care, patients receiving spinal anaesthesia will resume oral feeding on the same day of surgery and would hence not miss any statin doses. Selecting this population ensured that all studied patients were on statin therapy that was not discontinued perioperatively.

We used the inverse probability of treatment weighting (IPTW) method to control for observed confounding between the compared groups. As shown in Table 1 and Fig. 2, this method allowed us to better balance patients on individual covariates and decrease the absolute standardized differences (ASD) between the groups. Specifically, we estimated the probability of being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (*vs* non-user) as the outcome and using the all prespecified potential confounding variables listed in Table 1 as the predictors. Then, we calculated the weights as follows: the weights for statin users are $(\text{propensity score})^{-1}$; the weights for non-users are $(1 - \text{propensity score})^{-1}$. Comparison between statin users and non-users was made in separate models in which each data row (one patient per row) was weighted by the estimated propensity score.

Success of the control for confounding was assessed by comparing groups, after weighting on all the potential confounding variables used to construct the propensity score with the standardized difference (difference in means or proportions divided