after the procedure. Luo et al[4] demonstrated a 50% decrease in PEP by routinely using rectal indomethacin as opposed to using it only in selected high-risk patients. Routine rectal indomethacin use is a simple, safe, inexpensive modality to decrease PEP as the most frequent adverse event of ERCP. Although the authors make a compelling argument for the use of rectal indomethacin for "high-risk" patients, we must remember that the risks for PEP are additive, encompassing a spectrum of patient and technical factors. Perhaps the gap between "average-risk" and "high-risk" patients for PEP remains smaller in practice than is statistically elucidated. Therefore, the use of routine precautionary measures such as rectal indomethacin should be the new standard of care.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

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http://dx.doi.org/10.1016/j.gie.2016.10.023

Lowering the risk of post-ERCP pancreatitis

To the Editor:

We read with interest the meta-analysis of prospective randomized control trials examining the efficacy of rectal indomethacin for prevention of post-ERCP pancreatitis (PEP) in high-risk and average-risk patients published in *Gastrointestinal Endoscopy* by Inamdar et al.[1] They demonstrated that indomethacin reduced PEP in high-risk patients. However, they concluded that among average-risk patients the rate of PEP was similar and not statistically significant (relative risk [RR], 0.74; 95% confidence interval [CI], 0.52-1.07). The total number of average-risk patients was 2313. Our recent publication,[2] inclusive of 4017 total patients, coupled with that of Luo et al,[3] likely alters these conclusions because they studied larger cohorts.

Both studies demonstrate the benefit of rectal indomethacin in average-risk patients and were not included in the meta-analysis. Luo et al[3] demonstrated significant benefit with the universal use of rectal indomethacin compared with a risk-stratified strategy (RR, 0.47; 95% CI, 0.34-0.66) in 2600 patients. Our subsequent pragmatic retrospective cohort study reported on 4017 patients (3370 considered to be at low risk) who underwent ERCP; the study used propensity score matching and logistic regression to compare patients who received indomethacin with patients who did not.[2] We demonstrated that indomethacin significantly lowered the risk of PEP by 65% (odds ratio, 0.35; 95% CI, 0.24-0.51; $P < .001$). Both of these trials demonstrated significant benefit with rectal indomethacin without an increase in adverse events in patients who are not considered to be at high risk.

We are concerned that the lack of inclusion of these large studies, which included large numbers of low-risk to average-risk patients (5970 total), changes the validity and conclusion of the study by Inamdar et al. We hope to avoid, in as many patients as possible, the unfortunate occurrence of PEP; we believe that our data and those of Luo et al are sufficient to alter clinical practice to the routine use of indomethacin in all patients undergoing ERCP.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

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http://dx.doi.org/10.1016/j.gie.2016.10.024

Response:

We thank the authors[1-3] of the various letters for their interest and comments on article "Rectal indomethacin is protective against post-ERCP pancreatitis in high-risk patients but not average-risk patients: a systematic review and meta-analysis."[4] This is a topic of significant debate, and we appreciate the opportunity to respond.

A common theme in the letters was the lack of inclusion of a large study from China.[5] In our meta-analysis we provided exact details about the exclusion of this large study in the discussion section. Briefly, the Chinese study was designed to evaluate the efficacy of timing of administration of the drug. Patients were randomized to a strategy of drug administration. There was a universal group in which every patient received the drug before the procedure and a high-risk group in which high-risk patients received the drug after the procedure. The patients were not randomized to the drug versus placebo because the study evaluated a strategy of drug administration rather than drug efficacy. Therefore, the study did not meet our inclusion criteria.

He et al[3] also question the exclusion of another study from Iran.[6] That study compared the effect of rectal indomethacin and intravenous hydration in the prevention of post-ERCP pancreatitis (PEP). The study focused on multiple strategies with and without intravenous hydration or indomethacin for the prevention of PEP. It did not differentiate between average-risk and high-risk patients and, thus, was excluded from our meta-analysis. Thiruvengadam et al[1] also comment on the exclusion of another recent study by their group.[7] Unfortunately, even though that was a large study, it was a retrospective cohort study. Our meta-analysis sought to only include randomized controlled trials (RCTs) to control for the inherit limitations of retrospective studies.

We appreciate the comments by Barkin et al[2] regarding the definitions of "high-risk" and "average-risk" patients for PEP. The definitions used in our study were based on accepted definitions already used in the medical literature. The same definitions were used in the landmark study by Elmunzer et al.[8]

He et al[3] specifically address the issue of sensitivity analyses with the pooled estimates being significant after the exclusion of the study by Levenick et al.[9] The other RCTs in the meta-analysis devoted to average-risk patients show a combined positive effect of rectal indomethacin. Given that 1 study changes the results and is not the largest of the studies included, this shows that the positive effect seen is not very strong. This challenges the notion of the positive effect of this drug in this average-risk group. We think this demonstrates the need for additional well-designed studies similar to the study by Levenick et al.[9]

In conclusion, this meta-analysis of rectal indomethacin reaffirms its effectiveness in preventing PEP among high-risk patients, but the data are insufficient at this time to enable a conclusive recommendation for its use in all average-risk patients. Given the positive safety profile of rectal indomethacin, we do understand the argument for administration to every patient undergoing ERCP without contraindications to the drug; however, we do not believe that the evidence supports this practice, as demonstrated by this meta-analysis. We encourage larger, multicenter studies that would examine the use and timing of rectal indomethacin in average-risk patients, as several letter writers have suggested.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

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