End of the Road for Epinephrine Spraying of the Papilla to Prevent Post-ERCP Pancreatitis?

Mark A. Gromski and Evan L. Fogel

Indiana University School of Medicine, Division of Gastroenterology and Hepatology, Indianapolis, IN, USA

Endoscopic retrograde cholangiopancreatography (ERCP) remains the endoscopic intervention that is routinely performed by gastroenterologists which carries the highest risk of serious adverse events, the most frequent of which is post-ERCP pancreatitis (PEP). Substantial efforts have been undertaken to further the science of patient selection and prophylactic measures to reduce the risk of PEP. Yet, the rate of post-ERCP pancreatitis remains 3-15%, dependent upon patient, procedure and provider risk factors.[1]

In the current issue of *Clinical Gastroenterology and Hepatology*, Luo and colleagues describe their study regarding rectal indomethacin and spraying of the duodenal papilla with epinephrine to decrease the risk of PEP.[2] Ten centers in China took part in this prospective, randomized, double blinded study of 1158 patients undergoing ERCP with a native papilla. The patients were randomized in a 1:1 manner to receive either rectal indomethacin with saline papillary spraying or rectal indomethacin with epinephrine papillary spraying. Each patient received a single 100mg rectal suppository of indomethacin 30 minutes prior to ERCP. Just prior to removal of the duodenoscope at the conclusion of the ERCP, the endoscopist sprayed either 20 ml of saline or 20 ml of 0.02% epinephrine on the major papilla with a focus on the

This is the author's manuscript of the article published in final edited form as:
Gromski, M. A., & Fogel, E. L. (2019). End of the Road for Epinephrine Spraying of the Papilla to Prevent Post-ERCP Pancreatitis? Clinical Gastroenterology and Hepatology. https://doi.org/10.1016/j.cgh.2018.12.043

pancreatic duct orifice. The primary endpoint was the incidence of PEP. Based on pre-study sample size calculations, the target recruitment was 3,300 patients. At an interim analysis, however, it was found that PEP developed more frequently in the group with rectal indomethacin with epinephrine spraying of the papilla (8.5%) compared to the group with the rectal indomethacin and saline spraying of the papilla (5.3%, $p = 0.03$). Since the data met the pre-specified futility boundary and there was a significant unexpected increase in risk in the intervention group (indomethacin + epinephrine spraying), the study was terminated. The authors correctly point out that the trial was underpowered to draw an absolute conclusion that the combination therapy increased the risk of PEP, as it was stopped early after one-third recruitment.

This study was a well-designed, multi-center prospective randomized study with over 1100 patients. The endoscopist was able to place a protective pancreatic duct stent or administer aggressive post-procedural hydration for PEP prophylaxis, at their discretion. There were no statistical differences in usage of these additional adjuvant modalities between the two intervention groups. The mean BMI in this study was 22 kg/m^2, which is significantly lower than the average patient encountered at a Western endoscopic center. Otherwise, the indications, failed cannulation rate (2-3%), proportion of high risk patients (36%) and trainee involvement (>50%) would be consistent with a US academic practice.

Three previously published trials have studied PEP rates with spraying of epinephrine on the major papilla.[3-5] In one study by Matsushita et al, 370 patients undergoing ERCP were randomized to either 10 ml of 0.02% epinephrine sprayed on the papilla or sham saline spray.[3] This study involved only patients undergoing diagnostic ERCP, and the overall PEP rate was 1.1%.[3] There were no significant differences in PEP between the groups. However, the low PEP rate and underpowering of the study were clear limitations. In another study by Xu et al, patients undergoing ERCP were prospectively randomized to either 20 ml of 0.02% epinephrine or saline sham spray of the papilla.[4] Again, this study was limited to diagnostic ERCP procedures only. The authors found a significant difference in PEP between the groups, with 6.45% in the sham group and 1.95% found in the epinephrine intervention group (p=0.0086).[4] Methodological concerns, including mandated pancreas enzyme measurements twice in the first 24 hours post-ERCP, likely led to PEP rates higher than expected for diagnostic-only ERCP. A more recent study evaluated 192 patients who were randomized into one of three treatment groups: rectal indomethacin, epinephrine spraying of the papilla and combination therapy with both rectal indomethacin and epinephrine spraying.[5] Although a pilot study and clearly underpowered to draw firm conclusions, the authors note that there were fewer absolute cases of PEP in the groups including epinephrine spraying compared to indomethacin alone.

In the current study, Luo and colleagues [2] offer potential mechanisms of action for epinephrine spray for PEP prevention, namely topical application of epinephrine can induce arteriolar vasoconstriction, decreasing the tissue edema around the pancreatic duct orifice. This

in turn might reduce pancreatic ductal outflow obstruction. However, this mechanism of action of topical epinephrine sprayed on the papilla is difficult to grasp. The effect of a topical agent sprayed on the surface of the papilla would likely be extremely transient, as the flow of bile, pancreas juices and gastric juice effluent would quickly disperse this. One would suspect that the vasoconstricting effect of epinephrine would cause a local decrease in bloodflow, which may impair the delivery of indomethacin. For these reasons, this intervention has not been broadly adopted by Western endoscopists. We agree with the authors' suggestion that studies evaluating the biodistribution of indomethacin with or without papillary epinephrine spray would be of interest.[2] Additionally, a recent multi-center, prospective randomized trial compared the use of rectal indomethacin plus sham spray to rectal indomethacin plus epinephrine papillary spray in 959 patients who were deemed high risk for PEP.[6] This study, to date presented only in abstract form, found no difference in PEP between the epinephrine (6.7%) and sham (6.4%, $p = 0.87$) groups. Confirmation of these preliminary data is awaited.

The design of the current study was to compare the efficacy of a prescribed combined prophylactic measure (rectal indomethacin + papillary epinephrine spray) to a single prescribed prophylactic measure (rectal indomethacin + sham spray) to prevent PEP. This study highlights the current reality of PEP prevention. It is notable that a patient in this study may have received four prophylactic interventions intended to decrease the risk of PEP: rectal indomethacin, epinephrine spraying of the papilla, aggressive post-procedure intravenous hydration with lactated Ringer's solution and a protective pancreatic duct stent. It needs to be emphasized that the primary objective of this trial was to test whether the combination of

indomethacin and epinephrine was superior to indomethacin alone in PEP prevention. The study was not powered nor designed to detect a benefit (or harm) of these additional interventions. This underscores the current climate PEP prevention with the institution of multiple prophylactic measures in high risk patients. However, based on the results of this study, it may be time to discard the practice of topical spraying of epinephrine for PEP prophylaxis. Given the potential for harm to patients in the epinephrine group in this study, it will be difficult to justify pursuing this intervention in future studies with combination prophylaxis measures, given ethical considerations. Nonetheless, unanswered questions remain regarding multimodal therapy for PEP prophylaxis, including combinations of rectal indomethacin, pancreatic duct stenting and aggressive weight-based lactated Ringer's solution. Prospective trials are ongoing in an attempt to get a clearer understanding of the most effective strategy.

In summary, the current study by Luo and colleagues demonstrates no additional benefit with reduction in PEP in patients receiving rectal indomethacin with papillary epinephrine spray compared to rectal indomethacin with sham saline spray. Indeed, an increased PEP rate was seen in the combination arm. Credit should be given to the authors for a well-designed study that was well-powered and had a carefully devised interim analysis plan, which was carried out as intended. This study demonstrates that, despite advances in PEP prophylaxis over the years, there may be prophylactic PEP strategies left to be debunked. While it can't be said that this study rings the death knell for epinephrine spray to prevent PEP, enthusiasm will now certainly wane.

References

1. Leerhoy, B. and B.J. Elmunzer, *How to Avoid Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis.* Gastrointest Endosc Clin N Am, 2018. **28**(4): p. 439-454.
2. Luo, H., et al., *Rectal Indomethacin and Spraying of Duodenal Papilla with Epinephrine Increases Risk of Pancreatitis Following Endoscopic Retrograde Cholangiopancreatography.* Clin Gastroenterol Hepatol, 2018.
3. Matsushita, M., et al., *Epinephrine sprayed on the papilla for prevention of post-ERCP pancreatitis.* J Gastroenterol, 2009. **44**(1): p. 71-5.
4. Xu, L.H., et al., *Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis by epinephrine sprayed on the papilla.* J Gastroenterol Hepatol, 2011. **26**(7): p. 1139-44.
5. Hatami, B., et al., *Epinephrine in the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Preliminary Study.* Case Rep Gastroenterol, 2018. **12**(1): p. 125-136.
6. Kamal, A., et al., *541: A Randomized Trial of Rectal Indomethacin and Papillary Spray of Epinephrine Versus Rectal Indomethacin Alone for the Prevention of Post-Ercp Pancreatitis in High Risk Patients.* Gastrointest Endosc, 2017. **85**(5): p. AB78-AB79.