Author's response to reviews

Title: Emergency open cholecystectomy is associated with markedly lower incidence of postoperative nausea and vomiting (PONV) than elective open cholecystectomy: a retrospective cohort study.

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Author's response to reviews: see over
Re-submitted is a copy of the manuscript now entitled “Emergency open cholecystectomy is associated with markedly lower incidence of postoperative nausea and vomiting (PONV) than elective open cholecystectomy: a retrospective cohort study.” by Jeffrey M. East and Derek IG Mitchell.

We are grateful to the reviewers for their comments and will proceed to address all of them.

Reviewer 1 – Dr. D. Ionescu
1) “However only the minor corrections have been done to the initial manuscript”. The initial manuscript was extensively and substantially edited and all comments of both reviewers were addressed. The other reviewer agrees.
2) “I would suggest to the authors to have a better well established protocol and comparable study groups. It is true they can compare study groups with a different size but the groups in the present study are different in protocol also”. The study protocol is a well established, internationally accepted and standardized design. We do not understand what the reviewer means by saying that the groups are different in protocol. We are happy that the reviewer agrees that comparison groups do not have to be of the same size. We addressed the reviewers insistence that groups should be comparable by way of variables in our previous response – not only is it impossible to achieve perfect comparability of more than one or two variables between groups in any study, retrospective or prospective, it is undesirable because you cannot then determine the effect of the matched variable on the outcome you are studying – in this study we have chosen to match only the variable “surgical approach” (ie, open approach). Multivariable regression is a well established and accepted technique for adjusting the final statistical model for differences in variable frequency between groups – indeed, that is why the technique was invented. The study would have remained valid even if we had not matched for surgical approach but rather had adjusted for that variable (open versus laparoscopic) in the multivariable logistic regression equation.
3) “Besides, as I have mentioned in my previous report if the final goal is to compare emergency procedure with elective ones is no need to have separate data from all participant hospitals admitting that the protocol was similar. In fact a retrospective study is carrying this risk”. As we indicated in our previous response, it is absolutely essential to the integrity of this paper that the data for each hospital is tabulated and analyzed separately before pooling for the summary analysis. It is not statistically legitimate to pool data from different centers until interaction-by-center is excluded and therefore the data must be tabulated separately – this is standard practice in studies involving multiple centers. Moreover, as we also pointed out in our previous response, one of the major strengths of our study is the demonstration that the association observed is as profound at both hospitals – if the effect was only observed at one hospital, we would have had no basis for reporting these findings at all because the effect could then be attributed to some peculiar, hospital based confounder.
4) “a very high percentage of NG tube with no description of the criteria for NG tube placement. Modern approach does very rare use NG tubes in both emergency and elective cases”. We have not described criteria for NG tube placement because we have no way of knowing what they were in the individual case. As we accepted in our previous response (admittedly to the other reviewer), NG tubes are rarely used in current surgical practice and some of these NG tubes were probably passed for no other reason than the well established reluctance of some older surgeons to change. But, as we also pointed out, the reason why NG tubes were used in individual cases is irrelevant – NG tube is treated just like any other variable in the multivariable statistical model, and, not surprisingly, has no effect whatsoever on the outcome of interest (PONV). This failure of NG tubes to impact PONV is well established in the literature.
5) “no description of the postoperative analgesia protocol: drugs, doses, intervals, VAS and so on. Analgesic protocol must be described for the first 24 h postoperatively and so the
incidence of PONV”. This comment was also addressed in our previous response to the reviewer. The drugs used are identified in table 1 as fentanyl, meperidine and morphine. Total dosage in the 24 hour period after surgery is also reported in table 1 in “meperidine equivalency units”, which is defined in the legend. The interval between dosages is not a recordable variable for a group of patients since it is not fixed and the route of administration was sometimes intravenous and sometimes intramuscular (anesthetists usually used the intravenous route in the early postoperative period whereas nurses used the intramuscular route on the wards) – if this is what the reviewer means by anesthetic protocol, we would again like to point out that we have not encountered any literature which indicates that the effect of opioids on PONV varies by either the interval between doses or the route of administration (see, for example, Bollish et al; Efficacy of patient-controlled versus conventional analgesia for postoperative pain. Clin Pharm. 1985 Jan-Feb;4(1):48-52). We maintain that total opioid dosage in the 24 hours after analgesia is a sufficient variable to represent the effect of opioids on PONV and this is how it is done in all of the studies that we have seen in which this effect is tested.

6) “there are differences in premedication use in study groups”. Premedication is recorded as a variable and is appropriately and adequately adjusted for in the multivariable regression equation.

7) “there are differences in time to first oral intake in study groups”. Time to first oral intake is recorded as a variable and would have been included in the multivariable regression equation except that, as pointed out in the manuscript, the mean time to first oral intake was more than 24 hours in both comparison groups and therefore could not possibly have had any effect on PONV (which is, by definition, vomiting in the 24 hour period after surgery).

8) “Perioperative protocol is not well defined and described”. Perioperative protocol, in so far as it is measurable as variables which can be applied in a statistical equation and in so far as it is plausibly associated with PONV, is very well defined and described.

9) “Criteria for acute cholecystitis are not well defined. There are no indicated reasons for which acute cases have been operated as opened procedures and not evaluated laparoscopically first. In these conditions it is very difficult to compare the study groups and to draw a pertinent conclusion”. The comparison is not between elective cholecystectomy and (emergency cholecystectomy for) acute cholecystitis – it is between elective open cholecystectomy and emergency open cholecystectomy, regardless of the indication for emergency cholecystectomy (as long as the primary disease being treated is cholelithiasis). We have pointed out in the manuscript that some cases of emergency cholecystectomy would have been done for acute cholecystitis and others for unrelenting biliary colic (in which there is usually no cholecystitis). Both indications for emergency cholecystectomy are associated with profound pre-operative nausea and vomiting. We have also explained in the second draft of the manuscript why the few cases of emergency cholecystectomy approached laparoscopically were excluded, why we had to consequently also exclude elective laparoscopic cases and why we do not believe that cases were selected for open cholecystectomy (versus laparoscopic approach). This exclusion of laparoscopic approach (or, alternatively, matching by open approach) makes for a more fair comparison between the groups but we would have expected the same results had we included laparoscopic operations and adjusted for surgical approach in the multivariable logistic regression equation.

10) “I suggest the authors a prospective study with a well defined protocol and clear end points for evaluation, even if having so many open elective cholecystectomies will take some time”. With respect, I do not see how we could have designed a prospective study to detect an effect which we did not know existed and which is not even suspected in the literature. It is now appropriate to design a prospective study to further look at the association identified in this retrospective study, and we have supported that suggestion in the manuscript. We are of the impression that most prospective studies (maybe all) derive the hypotheses they test
from observations made during prior retrospective studies. Secondly, there is no reason why a prospective study designed to verify the important observed association (between preoperative nausea and vomiting and suppression of PONV) need be restricted to open cholecystectomy cases – we have explained above why matching by surgical approach was done in this case.

11) “In the end I would however point out that there is an interesting observation that deserves a rigorous prospective study before advancing a theory on the possible mechanisms”. We accept the compliment. However we do not accept that it is unreasonable to speculate on the plausible mechanisms for the association discovered – that is how hypotheses are generated and new ground broken. After all, the argument that nicotine (reference 11) and cigarette smoking reduce PONV by inducing enzymes in the liver that metabolize opioids and other emetogenic drugs is no less speculative than our theory. And finally, any prospective clinical study which confirms the association observed would still not provide proof of cause and effect – that will require experimental studies.

Referee 2 – Dr. Paul Karanicolas

1) “Having said that, the fact remains that the design of the study is very limited in that it is a retrospective cohort study, relying on clinical records.” We have not contended otherwise, but maintain that it is on the basis of just such retrospective studies that hypotheses are generated. Retrospective studies such as this also serve to provide some ethical justification for testing hypotheses prospectively. I can’t imagine getting ethical approval for a prospective study, especially an experimental one, without some evidence that the association I am planning to investigate has been discerned from a prior minimal risk, retrospective study.

2) “Furthermore, the practice of these surgeons (open cholecystectomies for all urgent cases and many elective cases, NG tubes for many patients, etc), is very different than the standard of care in North America and limits the applicability of these findings”. We assume that what the reviewer intends by “applicability” in this context is “applicability to other settings” and therefore “generalizability”. With respect, we do not agree  that the findings are not generalizable because of local differences and preferences in surgical approach. Multivariable regression is a powerful technique that is able to adjust statistical equations for the effect of any measurable individual quirks that we might have as surgeons. Matching by surgical approach also has the effect of eliminating the effect of the variable “surgical approach” on the outcome. I would expect, unless we are missing the effect of some unknown confounder, that, based on the universality of the multivariable regression principle, a surgeon in New York comparing emergency laparoscopic cholecystectomy to elective laparoscopic cholecystectomy, without any NG tubes, ought to detect the same association that we detected looking at the open operation (with all of our unnecessary use of NG tubes).

3) “Finally, even if one believes the results of this study, it unfortunately has little clinical implication”. The clinical implications of this study are the same as the clinical implications of the successful use of nicotine patches to suppress PONV in former smokers (Ionescu et al, reference #11). If the association between pre-operative nausea and vomiting and suppression of PONV is confirmed and if our plausible theory is proven, that “emergency cholecystectomy” and nicotine patches work by exploiting this association, then application of a pre-operative, sub-clinical emetogen with a more benign side effect profile than nicotine ought to achieve the same effect.

Suggested changes:

1) “Change the term "risk" in the title to "rate" or "incidence". We will concede a change from risk to incidence but not rate. What is described here is a proportion or probability and (incidence) risk is the precise and appropriate measure. Although (incidence) rate is
sometimes used loosely to refer to proportion, it is an incorrect usage of the word. Rate properly refers to a measure of incidence in relation to time and is therefore not applicable here.

2) “The conclusion section of the abstract remains too long- the justification for the conclusion is not needed here, but the conclusion does need to be justified!” Point taken. The conclusion in both the abstract and the body of the manuscript have been shortened to reflect only the main findings and implications of the findings and the sentence “Shortcomings of retrospective studies notwithstanding, the profundity of the suppressive effect of emergency cholecystectomy on PONV risk after multivariable risk adjustment, demonstration of similarly profound effect at both hospitals and the greater than 95% power of the statistical model mean that the finding is likely to be valid” has been deleted. The conclusion now reads: “The incidence risk of postoperative nausea and vomiting is markedly decreased after emergency open cholecystectomy compared to elective open cholecystectomy. The study, by extrapolation, also identifies a paradoxical association between pre-operative nausea and vomiting, observed in 80.2% of emergency cases, and suppression of PONV. This association, if confirmed in prospective cohort studies, may have implications for PONV prophylaxis if it can be exploited at a sub-clinical level”.