Author's response to reviews

Title: Emergency open cholecystectomy is associated with markedly lower risk 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 risk 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) We are uncertain as to whether Dr. Ionescu is suggesting that there is no real research question because the study is a retrospective one or that there is no real question in this study. If the latter, then we think this is an unfair comment. In the “Background” section of our paper, it is very clearly stated (though not in these exact words) that the primary research question is “Is the risk of PONV after emergency open cholecystectomy the same as the risk after elective open cholecystectomy?”. The secondary question is “What is the variable among emergency cases that is responsible for the suppressive effect of emergency?”. We hope that Dr. Ionescu would agree that it is inelegant to state the research question in this direct and pedantic way and that most research papers do not.

2) (a) “Study groups should be comparable in size”. There is no such requirement from a statistical perspective. All statistical packages which calculate sample size for studies offer several options by way of different numbers in each comparison group for a given power requirement. Epi-Info, the well known statistical program from the CDC, allows ratios of up to 4:1 between comparison groups. Additionally, we have taken the advice of Frank Harrell (reference number 4) and included “hospital” as an explanatory variable in our final regression equation to further compensate for any additional bias resulting from the difference in sample sizes between hospitals.

“Comparing 175 elective cases vs. 91 emergency cases may mislead to some conclusions and sample size is 54”. We are surprised at this comment. Increasing the number in the emergency group from 54 to 91 considerably increases the power of the study to detect a PONV risk of 10% in the emergency group as significant at the 5% level – it does not decrease it, as Dr. Ionescu seems to be implying. This was a deliberate strategy to enhance the power of the study and to try to compensate for the inherent weakness of the retrospective design. Using 91 in the emergency group rather than 54 increases the power of the study from 80% (the internationally accepted norm) to greater than 95% (Epi-info, version 3.3.2). We felt that the discerning reader would have recognized this as a strength of the study (rather than a weakness) but it appears that we should be more explicit. The second sentence in the first paragraph of the “Discussion” section has therefore been rewritten to read “The shortcomings of retrospective studies notwithstanding, the fact that the effect is confirmed at both hospitals separately and the considerable increase in power achieved by including 91 cases (greater than 95% power) in the emergency group rather than the 54 cases recommended to achieve 80% power all provide strong support for its validity.”. We have also made a similar comment in the conclusion section.

(b) “BMI should be comparable in study groups.” We do not understand why Dr. Ionescu believes that BMI should be comparable in study groups. We assume that she is suggesting that the cases should be matched by BMI but know of no valid basis for such a recommendation. Matching is a statistical technique used to reduce the effect of a known confounder on the outcome being studied. Other techniques are exclusion and multivariable regression. BMI has not been consistently shown to be associated with PONV in studies in which it has been included as an explanatory variable hence it would not be a good matching variable in the first place. Secondly, the technique which we have used to study the possible confounding effect of BMI on PONV, which is to test it as an independent variable in our statistical analyses, is not only the most popular but also the most desirable method of dealing with confounding variables because the effect of the variable can thereby be
measured rather than being hidden. We believe that it is incumbent on the reviewer, not to dogmatically state opinion as if it were fact, but to indicate why she thinks that her suggested method of dealing with confounders is superior to ours.

(c) “Emergency criteria should be better defined: ie, acute cholecystitis with fever, increased leukocytes count, suggestive ultrasound examination and others”. “Emergency criteria”, as defined by Dr. Ionescu, are of no relevance to the research question we tried to answer in this study. Emergency cases are very clearly defined in our “Methods” section – our definition is completely independent of the laboratory findings in any given case and even of the reason for performing emergency cholecystectomy, as long as cholecystectomy was the primary operation and cholelithiasis (invariably established by ultrasound) the primary disease being treated. Having shown that emergency cholecystectomy was associated with reduced risk of PONV, we decided to look at any underlying variables which were common to emergency cases (not differences between them) that could explain the effect of emergency. We fail to understand how inclusion of variables such as white cell count, fever and ultrasound findings would enhance explanation of the effect of emergency. Even if we did decide to dissect the emergency group, white cell count and fever would certainly not be reliable parameters – most cases of acute cholecystitis (and biliary colic, whether associated with inflammation or not) do not evoke either leukocytosis or fever because these conditions are usually non-infective inflammations.

(d) “Preoperative medication and procedures especially for emergency cases should be detailed: ie, metoclopramide, naso-gastric tube, opioids”. Table 1 includes the “procedures especially for emergency cases”, as well as those for elective cases, in extensive, excruciating detail. There is absolutely nothing in the technique used by our anesthetists for emergency cases that has not been captured among the variables presented in Table 1. Did Dr. Ionescu actually read Table 1?

(e) “Table 1 should be redone and should include only emergency vs. elective cases and not the participating hospitals assuming that the protocols were similar. Table 1 should include anesthetic risk (evaluated as ASA risk) also”. Again, Dr. Ionescu states what we should do without explaining why. It is vital, if the results in a multicenter trial are to be pooled, that there be no significant differences between the centers with respect to the variables being studied (which reflect anesthetic technique, etc). Table 1 allows the interested reader to compare for himself the differences in approach between the 2 hospitals and to verify (without having to take our word for it) that the variables that are important are indeed not significantly different between hospitals. One of the strengths of this study is that the effect of emergency on PONV risk is not only profound in the pooled sample, but is also demonstrated to be of similar magnitude at both hospitals separately. It would be unacceptable to submerge the explanatory variables from the individual hospitals in a pooled, summary table and then declare their effect on the outcome at each hospital (table 2) in a separate one. Display of the individual hospital’s results is therefore vital to this manuscript.

Dr. Ionescu advises that we should include ASA risk as a variable but, again, does not say how the study would improve as a result. Has ASA risk ever been shown in any study to be a risk factor for PONV and therefore a potential confounder? We have not found any such evidence. Moreover, we have included comorbidity and age as variables which, though crudely, should parallel anesthetic risk.

(f) “authors must detail what were the opioids administered, dosages, postoperative analgesic protocol.” Again, table 1 (including the legend) includes all the detail requested by Dr. Ionescu and again we are forced to wonder if she looked at this table in detail. The legend indicates that there were 3 opioids used – fentanyl, meperidine and morphine and that the total dosage given from premedication to 24 hours postoperatively is recorded in table 1 as “meperidine equivalency units”, which is also defined in the legend. “Postoperative analgesic protocol” is not an analyzable variable – we felt that total opioid dosage, which is
an analyzable variable, would adequately reflect both dosage and frequency of administration.

(g) “postoperative management of the patients must be detailed: NG tube (when necessary, routine), antiemetics, time to oral feeding and time to patient’s ambulation”. Again, table 1 already has all of the important details requested by Dr. Ionescu and again we must ask if she looked at this table at all. NG tube use and time to oral feeding are clearly and loudly recorded in the table. Use of antiemetics is also clearly recorded under “PONV prophylaxis” and an explanation of the way in which they were administered is included in the legend. Therapeutic antiemetic was not recorded in the table (even though this data was collected) because, in this study, we had no interest in this variable – we simply wanted to know whether or not PONV occurred, not its response to therapy. Time to patient’s ambulation is not a recordable variable in a retrospective study (nor have we seen it recorded as a variable in prospective studies on PONV). Time to discharge from hospital is usually used as a proxy measure for early ambulation but in this study, no patient was discharged in the 24 hours post anesthesia and therefore our reasonable assumption was that early ambulation would not have been a significant confounder of effect of emergency on PONV, since PONV, by definition, only occurs during the 24 hours following the end of anesthesia. Time to first oral intake, as indicated above, is clearly recorded in the table and further, it is noted in the results section that early feeding could not have been a contributor to PONV in this study because the mean time to first feeding was well over 24 hours (the time period for diagnosing PONV).

(h) “anesthetic protocol should be detailed and comparable in study groups: ie the same percentage of using muscle relaxants (in authors Table 1 there are differences in % of patients where relaxants were administered), opioids dose should be comparable and detailed.” We cannot understand the relevance of detailing the anesthetic “protocol”. We have included every single drug administered by the anesthetists as a variable. Again, Dr. Ionescu insists on comparability of protocols, of % of patients where relaxants were administered and opioid dosage without indicating how the study would benefit from such matching. “Comparability” of anesthetic protocol, % of relaxant administered and opioid dosage cannot be ensured in any study, neither prospective nor retrospective, because those variables must be determined based on individual patient’s needs and the anesthetist’s judgment and cannot be predetermined and dictated in any study. With respect, Dr. Ionescu’s insistence on “comparability” of such a large number of variables, which is impossible in any study, leads us to wonder whether she accepts the well established statistical technique of multivariable regression which is used in this study to adjust the equation of effect for exactly those differences in “protocol” about which she is concerned.

(i) “PONV “on operating table” (page 5) must be defined: after recovery (extubation), before intubation?” The meaning of PONV on operating table is obvious and we do not see how it could be better defined. It means any episode of PONV occurring on the operating table, before the patient is moved to the recovery room. PONV, by definition, could not have occurred before intubation.

(j) “I suggest considering PONV in the first 24 h or separately in the first 24h and the next 48 h. I consider the first 72 h after operation for assessing PONV is a too long time interval and the patient should drink and eat at 72 h”. With respect, we do not know what to make of this comment. Nobody assesses PONV over 72 hours and we certainly did not indicate that we did. It seems as if Dr. Ionescu has misinterpreted our assessment of pre-operative nausea and vomiting during the 72 hour period preceding surgery with our assessment of PONV (post-operative nausea and vomiting) in the 24 hour period following completion of general anesthesia. We hope that we are incorrect about this latter assumption because it means that she would have misunderstood the most important conclusion of this study – that pre-operative vomiting is statistically associated with suppression of post-operative vomiting (PONV). This is very disconcerting.
PONV is defined internationally as vomiting or retching occurring within 24 hours of the end of general anesthesia – this is the definition used in all of the references cited and in this study – we did not make it up. We are not allowed to make up our own definition by extending the period for diagnosis of PONV to 48 hours. Definition of PONV is restricted to this 24 hour period because beyond that, nausea and vomiting is more likely to be due to causes other than drugs used during anesthesia, such as ileus, etc.

3) “Not enough details”. We do not know how to respond to this, except to say that everywhere in the preceding discussion that Dr. Ionescu has asked for more detail, we have been able to show that it was either already included in the paper or else it was not relevant to answering the research question. If anything, we have included too much detail because most of the variables included have been proven by previous studies to be unassociated with PONV.

4) “Must be detailed on some aspects and more concise on others”. No response is possible to this non-specific comment.

5) (a) “Not entirely. Discussions should be more focused on study findings and potential explanations. Incidence of findings should be reported to the literature findings”. No response is possible to these non-specific comments.
   (b) “History of motion sickness must be excluded from the analysis. Comments as “unlikely to be differentially distributed between two groups” (page 10) must be withdrawn once this factor is excluded.” We beg to humbly disagree with Dr. Ionescu. “History of motion sickness” was not included in the analysis – it could not be, because this variable was not recorded in patients’ notes and therefore could not be extracted as a variable. However, it must be included in the discussion on possible unmeasured confounders for the association between emergency and PONV because it is an established, major risk factor for PONV and constitutes one of the 4 major risk factors for PONV in Apfel’s risk score (the others being female gender, smoking history and narcotics). That it is unlikely to be differentially distributed between the comparison groups in this study is a very reasonable statement to make since there is no known association between history of motion sickness and biliary colic or acute cholecystitis, the usual diagnoses in patients having emergency cholecystectomy.

6) “The limitation of the studies is missing from Discussion section”. We did admit, in the second sentence of the first paragraph of the discussion section, that we expected the study to suffer from the usual, well known shortcomings of retrospective studies. However, we do agree now that this is not sufficient – 4 new paragraphs (2nd to 5th) have now been inserted into the discussion section which speak more specifically to all the shortcomings of the study.

7) “Not very clear. There are acknowledgements on conflict of interest and involvement in the study but not on similar publications”. The “Background” section of our manuscript is quite clear on this question – there are no prior studies that we could identify similar to this one and no prior studies seeking specifically to study the effect of emergency cholecystectomy (nor any other emergency operation for that matter) or of preoperative nausea and vomiting on PONV risk. We had hoped that the reviewer would have done her own literature search and either supported or denied our assertion that no similar studies exist. It is a bit disconcerting that the reviewer alleges that we did not acknowledge “similar publications” without identifying any that we might have missed. We also feel that we deserve some credit for acknowledging that the idea that preoperative stimulation of the vomiting centers might lead to adaptation did not originate with us, but with an editorialist in another journal.

8) “No. Both the title and the abstract must be focused on the findings of the study and not on prophylaxis (title) or discussions (abstract)”. We accept criticism of the title. The title has therefore been changed to read “Emergency open cholecystectomy is associated with markedly lower risk of postoperative nausea and vomiting (PONV) than elective open cholecystectomy: a retrospective cohort study.”
However, we feel very strongly that discussion of the implications of this finding for PONV prophylaxis is critical to the value of the manuscript and therefore should be retained in both the discussion and the abstract. Nevertheless, to improve focus on the findings and less on speculation, we have made the following changes:

(a) The ending of the final sentence in the results section of the abstract has been changed from “……present in 80.2% of emergency cases and probably operable at a sub-clinical level in the rest” to “……present in 80.2% of emergency cases in the 72 hour period preceding surgery”.

(b) The conclusion section of the abstract has been rewritten to read as follows: “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. The ostensibly paradoxical association between sustained preoperative nausea and vomiting and PONV suppression hereby identified, if confirmed in prospective cohort studies, may have implications for PONV prophylaxis by a mechanism other than receptor blockade.”.

9) “The writing should be more lapidary and precise. Finally, English language should be checked and improved: ie narcotic (should be replaced with opioids), acuity of operation, perusing, serendipitous.”. The first sentence is too nonspecific for a response. As for the second sentence:

(a) Narcotic is used interchangeably with opioids in every dictionary that we have checked. In fact, Steadman’s medical dictionary, although acknowledging that both terms are used interchangeably, point out that “opioids” ought to refer only to synthetic narcotics and not those derived from opium (such as morphine). In this respect, narcotic is therefore the more precise term.

(b) “acuity of operation” was meant to mean “acuteness of operation”, by way of urgency rather than preciseness. We did not invent this expression, adopting it from one of the cited references, but we agree that it is misleading and have replaced it where it occurs with “urgency of operation” or “emergency”.

(c) “perusing” means to examine in detail and has been used appropriately.

(d) “serendipitous” is used appropriately – the association identified in this study would not have been discovered but for the exploratory analysis mentioned in the “Background” section. It was completely unsuspected and is therefore a serendipitous or “lucky” discovery. Nevertheless, we have deleted it entirely.

Referee 2 – Dr. Paul Karanicolas

1) General Comments:

(a) We would like to suggest to Dr. Karanicolas that there are several reasons why he ought to have a little more confidence than he does that the findings are valid, despite the retrospective design. First the effect is really quite profound, too profound to be explained away by any of the sources of error inherent in this retrospective study and in the method of measuring the primary outcome. Although we would expect such errors to affect the absolute risk in each group, they ought to affect each group similarly and therefore should not have any significant effect on the comparison of risks (the odds ratio in this case). His assertion that reduced risk of PONV observed in emergency cases can be fully explained by reduced reporting by health care staff distracted by more prominent symptoms in this group (see below) is a bit of a stretch – this would require us to believe that such distractions as fever could explain reduced reporting of the order of 75% and that this reduced reporting could have occurred at 2 separate training institutions for nurses and anesthetists to almost exactly the same degree. Secondly, the effect is of the same order of magnitude at both hospitals – it would
seem to be very unlikely that this would happen if it was not a true effect. And thirdly, the power of this study is more than 95%, with the increase in the size of the emergency group to 91 (rather than the 54 cases recommended by Epi-Info for 80% power).

(b) We agree that our call for research into agents that might prevent PONV by the mechanism postulated to explain our findings is premature. We have therefore deleted the sentence which makes this call and reworded our conclusion to indicate that the findings should be confirmed in a prospective study. However, we feel that it is important to suggest that if this effect of “emergency” is confirmed in prospective studies, an agent which mimics its effect would have implications for PONV prophylaxis. The new conclusion section now reads: “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. The ostensibly paradoxical association between sustained preoperative nausea and vomiting and PONV suppression hereby identified, if confirmed in prospective cohort studies, may have implications for PONV prophylaxis by a mechanism other than receptor blockade.

(c) Dr. Karanicolas’s faith in the efficacy and sufficiency of drugs currently used for PONV prophylaxis is not supported by the literature. Reference 3, which is a Cochrane review, states in its conclusion that “Most patients given a drug to prevent nausea or vomiting after surgery will not benefit from it”. There are several other references in the literature which have found that some of these agents (including the much touted serotonin HT3 receptor antagonists) might be completely ineffective in preventing PONV. Two points follow from this observation. First, we are obliged to continue to try to identify more effective agents for PONV prophylaxis. Second, we need to identify additional pathways for PONV suppression, since the mechanism of receptor blockade seems to have run its course. We believe that our findings may be giving us a glimpse into a new pathway.

2) Specific Comments:

(a) The title has been revised and the statement regarding implications for PONV prophylaxis has been removed. The title now reads “Emergency open cholecystectomy is associated with markedly lower risk of postoperative nausea and vomiting (PONV) than elective open cholecystectomy: a retrospective cohort study”.

(b) The conclusion section of the abstract has been revised and shortened by 1/3. It is now more focused on defending the likely validity of the finding, on the need for confirming the finding in prospective research and on the implications of the research if the finding is confirmed.

(c) In Jamaica, emergency cases are not usually explored laparoscopically because of the high conversion rate (and therefore wasted operating time), the increased risk of common bile duct injury and the high cost of laparoscopic disposables. Even those surgeons who offer laparoscopic cholecystectomy as standard of care for elective cases continue to perform open cholecystectomy in all but a few emergency cases. So, there is no significant selection of emergency cases for performance of open cholecystectomy – they are almost all done that way. However we feel that we should address Dr. Karanicolas’s concern in the manuscript and this is done in 2 places. First, in the final sentence of paragraph 2 of the methods section: “Cases of laparoscopic cholecystectomy were also excluded, whether successfully completed or converted to the open operation,
because the laparoscopic approach was only rarely used to treat emergency cases at both hospitals and therefore including laparoscopic cholecystectomy cases in either comparison group could have introduced potentially significant selection bias”. It is again addressed as we discuss the likely impact of selection bias in a new 3rd paragraph in the discussion section, which reads “Selection bias also appears to be minimal, or at least unlikely to explain the profound effect observed. More than 90% of emergency cases over the data collection period were performed by the open method, even by surgeons who offer laparoscopic cholecystectomy as standard of care for elective cases. If there was any selection bias, it would therefore apply more to the small emergency laparoscopic group than to the emergency open group, hence the decision to exclude those emergency cases performed laparoscopically. Elective open cases were also not subject to significant selection, being performed predominantly by surgeons who do not offer the laparoscopic approach in their repertoir. Having decided that the emergency comparison group should only include open cases, the elective comparison group also had to exclude laparoscopic cases to ensure a fair comparison.”

(d) Dr. Karanicolas’s speculation that failure among care providers to record PONV is more likely if the patient has other distracting issues such as severe pain, fever and wound related issues, which are more likely to occur in patients who had emergent rather than elective cholecystectomy, was considered by us but not in relation to the symptoms that he suggests. That the difference in pain, temperature and “wound related issues” between elective and emergency cases could result in a greater than 75% reduction of recording of PONV in the emergency group and that this reduced reporting could have occurred at 2 separate training institutions for nurses and anesthetists to almost exactly the same degree requires a far greater degree of “belief” and imagination than accepting that the association we identified could be valid.

We spent quite a lot of time looking for possible reasons why PONV might be less likely to be reported by both patient and caregiver in emergency cases and we could not come up with a credible candidate. We felt that the greater use of NG tubes in the emergency group might be sufficiently distracting to result in reduced reporting in this group but the analysis does not indicate any association between NG tubes and PONV risk. Although a finding of no association may reflect negative confounding, the literature confirms our finding that there is no association between NG tubes and PONV.

We do not accept that selective reporting bias is a “much more compelling explanation of the study’s finding than the author’s hypothesis” and contend that this is an unfortunate and unsupported exaggeration by Dr. Karanicolas of the potential of this possible error. The fact is that there is no variable that we can conceive of, either measured or unmeasured, objective or subjective, that could account for such profound and uniform underreporting at both hospitals. However we have acknowledged in a new second paragraph in the Discussion section that this is a potential source of error in this study. The paragraph reads as follows: “The retrospective design might have resulted in underestimation of the true, absolute risks of PONV. It is unlikely that many instances of vomiting were missed or unrecorded, since recovery room charts have a section specifically for recording occurrence of PONV and since ward nurses meticulously record episodes of vomiting and retching (both hospitals are training institutions for nurses) as well as patient complaints (expected to capture most clinically significant episodes of nausea), but some episodes of nausea might not have been reported to nurses, particularly if transient and mild. Any reporting bias, however, would be expected to
affect both comparison groups equally at each hospital and should therefore not change the odds ratio for the effect of emergency at each hospital. No variable, measured or unmeasured, was identified which could plausibly explain any increased likelihood of underreporting of PONV in emergency cases, either by patients or nurses and anesthetists. If underreporting of PONV in emergency cases was a significant source of error, it would be extremely unlikely to manifest itself to almost the same degree at both hospitals. The remarkable similarity between the odds ratios for the effect of emergency at each hospital (0.2 at CRH and 0.14 at UHWI, P=0.82) certainly favors the more plausible explanation that there is some variable common to emergency cases which explains the effect observed”.

(e) Patients received NG tubes in the majority of cases (both elective and emergency, except elective at UHWI) because some of our surgeons are old fashioned and even if the surgeon is not, the nurses preparing patients for surgery are and it does take time to change nursing culture. If this study were conducted now, just 2 years later, the proportion of patients with NG tubes would be markedly lower. Some patients would have received NG tubes because of preoperative vomiting or because the surgeon still believes that “bowel rest” is part of the treatment of cholecystitis or to reduce the size of a stomach, distended by swallowed air, which was encroaching on the operating field. However, regardless of the reason they were used, NG tube was not associated with PONV in the statistical analysis (nor are they associated with PONV in the literature) and therefore Dr. Karamicolas’s implication that NG tubes could be a major confounder in this study is not supported at all. If he is merely criticizing our continuing use of a distressing modality that is unnecessary in the majority of cases, then we accept that criticism on behalf of our colleagues but it has no relevance to the findings of the study.

(f) Comments on possible error related to the timeframe over which data was collected was included in our first draft of the manuscript but was deleted from the submitted manuscript because we felt that the point was not worth making. First, the bulk of the data was collected over a time period common to all four groups. Second, for calendar period to be a plausible confounder in a study, some variable associated with outcome would have to have undergone some unmeasured change over the period. There is certainly no plausible evidence that the disease itself, its complications, treatment and indications for surgical treatment (and indications for urgent surgical treatment) would have changed significantly over this relatively short calendar period. What might have changed is the drugs used during anesthesia and this variable is amply captured and tested in our statistical analysis so that the effect of any confounding resulting from those changes would have been adjusted for. Again, Dr. Karamicolas exaggerates the potential effect of this error in his statement that “... this could explain the differences seen.”. By no stretch of the imagination could this error result in the profound effect observed, even if significant and even if it did not cancel out itself by having the same effect on both comparison groups.

Nevertheless, we have decided to indicate the time period over which the data was collected for each group at each hospital. The first sentence of the Results section now reads “Data were collected on 175 cases of elective open cholecystectomy, 150 from CRH (May, 2002 to May, 2007) and 25 from UHWI (March, 2001 to May, 2007), and 91 cases of emergency open cholecystectomy, 41 from CRH (January, 2002 to May, 2007) and 50 from UHWI (February, 2001 to May, 2007)”. We have also added a paragraph (the 5th) to the discussion section acknowledging that this is a possible source of error this paragraph reads as follows: “The bulk of the data for all groups was collected over a common time
period (May, 2002 to May, 2007) so there is little opportunity for error resulting from changes over time in either the disease or its treatment. Any changes in anesthetic technique would have been captured among the variables extracted and adjusted for in the analysis”.

(g) The risk of PONV observed among elective cholecystectomy cases (28.6%) are not “much lower than those commonly reported”. Several references in the literature indicate that the average range of PONV reported internationally is 20 – 30% (see Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia 1997; 52: 443-449). We believe that some of the more recent prospective studies may in fact be overestimating the risk of clinically significant PONV by inadvertently including other types of unpleasant postoperative phenomena such as dysphoria and anorexia (from gastric distension) and by overemphasizing a patient interview component (which seeks to elucidate nausea during a period when most patients are likely to be still sedated and subject to impairment of short term memory). Secondly, reliance was not placed on the recording of PONV by “members of the treating team”, although it was noted when recorded. As indicated clearly in the methods section, reliance was placed on recordings by anesthetists, nurses and doctors (who were predominantly interns and junior residents) who would not have had any vested interest in under-recording episodes of PONV. We don’t understand why Dr. Karanicolas believes that this “is a major problem”.

(h) We never said that our conclusions “are valid” and we certainly did not posit the results of the multivariable regression analysis as the main or only reason for our statement re validity. We said that they are “likely to be valid” which is not the same as the statement of certainty attributed to us by Dr. Karanicolas. Additionally, our conclusion though supported by the fact that the effect persisted and in fact increased after adjustment for confounders, was not only based on this finding from the statistical analysis. The main reasons why we believe that our results are “likely to be valid” are “the profundity of the suppressive effect of emergency cholecystectomy on PONV risk, demonstration of similarly profound effect at both hospitals and the greater than 95% power of the statistical model” (see conclusion section of abstract).

We however agree with Dr. Karanicolas that our “suggestion that emetogens should be tested as a result of this study is not supported” and instead, have called for confirmatory prospective studies to test the validity of our finding of an association between preoperative nausea and vomiting and reduced risk of PONV.

However, we hope that Dr. Karanicolas can agree with us that the study in which preoperative nicotine patches successfully suppressed PONV risk (reference 11) does also demonstrate an association between preoperative emetogenesis and suppression of PONV risk (though not necessarily a cause and effect relationship) and that this could turn out to be an interesting potential pathway that could be exploited, if it is proven to be valid, with potential benefit for patients.