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

Authors:

    Jeffrey M East (jeast@cwjamaica.com)
    Derek I.G. Mitchell (derekigmitchell@gmail.com)

Version: 3  Date: 4 October 2009

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) 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 have made every effort to make these questions clear in our “Introduction” without stating them explicitly, which we think would be inelegant.

2) (a) “Study groups should be comparable in size”. With due respect, study groups are not required to be comparable in size. 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 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 5) 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. It is fortunate that valid statistical comparisons can be made between groups of different sizes – in the instant case, for example, it allows us to compare outcomes between 2 operations, one of which is performed much less frequently than the other.

“Comparing 175 elective cases vs. 91 emergency cases may mislead to some conclusions and sample size is 54”. Increasing the number in the emergency group from 54 to 91 was a deliberate strategy to increase the power of the study to detect a PONV risk of 10% in the emergency group as significant at the 5% level, thereby further decreasing the probability that the observed difference could be due to chance. 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 have decided to explain this strategy in the second sentence of the first paragraph of the “Discussion” section which now reads “The well known shortcomings of retrospective studies notwithstanding, the profundity of the suppressive effect of emergency after adjustment for plausible confounders, the fact that the magnitude of the effect is similar 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 required 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 assume that the reviewer is suggesting that the cases should be matched by BMI. 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. 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 (which it would be if there was matching on BMI). BMI has not been shown in the literature to be a risk factor for PONV.

(c) “Emergency criteria should be better defined: ie, acute cholecystitis with fever, increased leukocytes count, suggestive ultrasound examination and others”. Emergency cases are defined in our “Methods” section – our definition is 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. With due respect to the reviewer, the “emergency criteria” she outlines would identify differences between emergency cases (rather than similarities) and would therefore be unhelpful in explaining what appears to be an outcome common to emergency cases in general.

(d) “Preoperative medication and procedures especially for emergency cases should be detailed: ie, metoclopramide, naso-gastric tube, opioids”. Table 1 displays variables reflecting all of the drugs used and procedures performed on all cases, both elective and emergency. There is no drug or technique used by our anesthetists for emergency cases that has not been captured among the variables presented in 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”. It is essential, 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/herself 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 essential for the credibility of this manuscript.

ASA risk has not been shown in the literature to be a risk factor for PONV and therefore was not assessed as a potential confounder. However, comorbidity and age are included as variables and these, though crudely, should parallel anesthetic risk.

(f) “authors must detail what were the opioids administered, dosages, postoperative analgesic protocol.”. Table 1 (including the legend) includes all the detail requested by Dr. Ionescu. 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. The variable “total narcotic” was meant to capture dosage as well as frequency of administration and therefore, indirectly, “analgesic protocol”.

(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”. Table 1 has all of the important details requested by Dr. Ionescu. NG tube use and time to oral feeding are both recorded. Use of antiemetics is also 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 was not a recordable variable in this retrospective study. 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 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.” Every drug administered by the anesthetists is recorded as a variable.

“Comparability” of anesthetic protocol, % of relaxant administered and opioid dosage could not be ensured in this retrospective study and we believe that it would be difficult even in a prospective study because these variables must be determined based on individual patient’s needs and the anesthetist’s judgment and cannot be predetermined nor dictated in any study protocol. As indicated previously, we have chosen to use the accepted technique of multivariable regression to deal with the possible confounding effect of these variables rather than matching (or comparability).

(i) “PONV “on operating table” (page 5) must be defined: after recovery (extubation), before intubation?” The following definition of PONV on operating table has been inserted in parenthesis: “..that is, after end of anesthesia but before and during transfer to recovery room”.

(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 believe that Dr. Ionescu may have misread 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. PONV is defined as vomiting or retching occurring within 24 hours of the end of general anesthesia – this is the definition used in all of the relevant references cited and in this study. 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”. With respect, we believe that we have provided all the detail necessary – we cannot think of any detail that has been omitted.

4) “Must be detailed on some aspects and more concise on others”. With respect, we believe that we have provided all the detail necessary. We have also reviewed the entire manuscript and tried to eliminate redundancy where it occurs.

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”. We have tightened up the discussion to focus more on the findings and less on speculation about the implications of the research. Systematic and repeated search of the literature did not turn up any other papers looking at the effect of emergency cholecystectomy on PONV risk nor any identifying the apparently paradoxical association between preoperative vomiting and suppression of PONV, except for those on the effect of nicotine and cigarette smoking. There were therefore no other papers to compare our findings to.

(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 respectfully 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 cannot be excluded from the discussion on possible unmeasured confounders for the association between emergency and PONV because it is an established, major risk factor for PONV, constituting 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 accept this criticism and have added 4 new paragraphs (2nd to 5th) to the discussion section which speak 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”. As indicated above, 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.

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 this criticism. 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.”. Our discussion of the implications of this finding for PONV prophylaxis has been retained but has been toned down. In order 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 subclinical 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.”. We have made the following changes:

(a) Narcotic is usually used interchangeably with opioids in the literature. Nevertheless, we have decided to change narcotic to opioid wherever it occurs in the manuscript as a noun.

(b) “Acuity of operation” was meant to mean “acuteness of operation”, by way of urgency rather than preciseness. We adopted this expression from one of the cited references, but we agree that it could be misleading and have replaced it where it occurs with “urgency of operation” or “emergency”.

(c) With respect, we believe that “perusing” has been used appropriately.

(d) We have deleted “serendipitous” even though we believe that it was used appropriately.

Referee 2 – Dr. Paul Karanicolas

1) General Comments:

(a) There are three reasons why we believe that our findings are likely to be valid. 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). Postulation that the reduced risk of PONV observed in emergency cases can be explained by reduced reporting by health care staff
distracted by more prominent symptoms in this group (see below) is a reasonable one but it is highly unlikely that distractions, such as fever or more severe postoperative pain (which would only be present, if at all, in a small minority of emergency cases) 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 (this point is addressed in greater detail below). So the second reason for believing that the effect is likely to be valid is that it is of the same order of magnitude at both hospitals – it seems 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) The efficacy of drugs currently used for PONV prophylaxis (and therapy) is far from perfect and therefore the search continues for more effective agents. 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 (although this is changing) 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 (which is money wasted when conversion becomes common). 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. Karanicas’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 repertoire. 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) The very reasonable speculation that failure among care providers to record PONV may be 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. Indeed we sought diligently to find proxy variables that statistically explain this possible bias. That the difference in pain, temperature and “wound related issues” (to the extent that they exist at all) 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 must be extremely unlikely. 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 (that is, reported 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, respectfully, 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 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 multivariable statistical analysis and therefore cannot be considered a significant confounder. Although this does not entirely rule out the possibility that NG tube could be a confounder, since its effect could have been masked by another untested, unknown, related confounder, the literature strongly supports the finding that NG tubes are not associated with reduced PONV (which is one of the reasons most of us have abandoned them in the first place).

(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 we could not argue for it being a significant potential source of error. 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. We do not therefore believe that there is any bias from this source but even if there is, it could not possibly be of sufficient strength to result in the profound effect observed.

Nevertheless, we have decided to indicate the time period over which the data was collected for each group at each hospital and comment on this as a possible source of error. 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).” The new, 5th paragraph of the discussion section acknowledging that this is a possible source of error 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%) is actually at the upper end of the average, internationally reported risk of 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 and distortion of short term memory).

Secondly, though we agree that in theory, an independent team of observers in a prospective study might have recorded a higher risk by being attentive entirely to this outcome and to nothing else, we respectfully do not agree that members of the treating team (and nurses in particular) might be motivated to significantly under-record episodes of PONV since PONV cannot be considered the fault of team members.

(h) The multivariable regression analysis per se is not the main or only reason for our statement re the “likely” validity of our observation. Three reasons were given above why we believe that our findings are “likely” to be valid. We repeat them here. 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 (which actually increases after multivariable regression), 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 believe that it is not unreasonable to suggest that the study in which preoperative nicotine patches successfully suppressed PONV risk (reference 11) does actually demonstrate an association between preoperative emetogenesis (nicotine being a potent emetogen) and suppression of PONV risk (though not necessarily a cause and effect relationship) and that this could turn out to be an interesting potential alternative pathway that could be exploited, if it is proven to be valid, with potential benefit for patients.