

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Surgical quality in organ procurement during day and night; an analysis of quality forms
AUTHORS	de Boer, Jacob; Bogt, Koen van der; Putter, Hein; Ooms-de Vries, Kirsten; Haase-Kromwijk, Bernadette; Pol, RA; Jonge, Jeroen de; Dejong, Kees; Nijboer, Mijntje; Vliet, Daan van der; Braat, Dries

VERSION 1 – REVIEW

REVIEWER	Chris Callaghan Consultant Transplant Surgeon, Guy's Hospital, London, UK
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	<p>This interesting study addresses the important issue of a possible association between time of organ procurement surgery and procurement-related injuries. This is a topic of considerable interest to surgeons and patients, and health administrators.</p> <p>The study is generally well written, and clear, and the conclusions are balanced and based on the findings of the study.</p> <p>The authors should consider the following:</p> <p>1) The study was performed over a relatively short time period (just 18 months), and almost 5 years ago. Can the authors comment on why they didn't utilise a longer study period (which presumably would result in more damage events, and better statistical power)?</p> <p>2) Can the authors comment on the surgical experience of the procuring surgeon? Can they be confident that procurements performed during the day weren't performed by more experienced surgeons? If a procurement was performed in a large academic transplant centre during the day, it might be possible that a more senior surgeon might be involved. Were the procuring surgeons all on-call for 24 hours? More information on the rota of these surgeons and how this might affect the findings would be useful.</p> <p>3) The authors state that the implanting centres' opinions on the forms took precedence if there was variance between the procuring and implanting teams. Often the organs will be procured and implanted by members from the same transplant unit; sometimes the organs will be exported to another team. Could this introduce bias - e.g. exported organs might be more likely to be coded as damaged if</p>
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	<p>they came from other teams? Is the proportion of exported organs the same for day and nighttime procurements?</p> <p>4) There are multiple other papers that look at risk factors for procurement-related injuries that have not been referenced, including:</p> <ul style="list-style-type: none"> - Kidney damage during organ recovery in donation after circulatory death donors: data from UK National Transplant Database. Ausania F, White SA, Pocock P, Manas DM. Am J Transplant. 2012 Apr;12(4):932-6. - Liver damage during organ donor procurement in donation after circulatory death compared with donation after brain death. Ausania F, White SA, Coates R, Hulme W, Manas DM. Br J Surg. 2013 Feb;100(3):381-6. - A registry analysis of damage to the deceased donor pancreas during procurement. Ausania F, Drage M, Manas D, Callaghan CJ. Am J Transplant. 2015 Nov;15(11):2955-62. <p>These papers should be appropriately referenced. In addition, the risk factors for organ damage identified in these papers (e.g. presence of aberrant anatomy) should be taken into account. The authors state that this should be evenly distributed across day/night procurements, but this should be checked and corrected for.</p> <p>5) How can the authors exclude organ damage from trauma that occurred prior to procurement in their analysis, e.g. motor vehicle accidents?</p> <p>A more minor point:</p> <p>6) Page 12 of 25, line 13. This sentence refers to the start time of surgery, though some readers may not note that the definition used is time of aortic cross-clamp. It would be useful to state this clearly in this sentence.</p>
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REVIEWER	Paul Chestovich UNLV School of Medicine, Las Vegas, NV
REVIEW RETURNED	13-May-2018

GENERAL COMMENTS	<p>The authors have done a nice study investigating surgical damage occurring during abdominal organ procurement as it relates to the time of procurement. This is a very simple and nicely done study. My comments and questions are below.</p> <p>Context of using “on one hand” and “on the other” is incorrect. This would probably be better phrased as follows. “It is difficult to relate a specific surgical injury to a particular negative outcome in a patient, because not all intra-operative injuries are noticed and negative outcomes are multifactorial and complex. Final sentence of introduction, “relationship” instead of “relation” would be more appropriate.</p> <p>While it can be assumed that vascular anatomy should be equal across the patient distribution, anomalies and clusters of abnormalities can still exist. I suspect that the information on any vascular abnormalities or other factors impacting the operation should exist on the quality forms. It would be helpful if this data were included, should it be available, and actually show that the vascular abnormalities are the same in each group.</p> <p>The only confounders analyzed are age, height, weight, BMI, sex and donor type. There are other confounders which might make</p>
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	<p>procurement more difficult (i.e. previous surgery leading to adhesions).</p> <p>While treating surgical injury as a binary outcome (yes/no) is ideal for simplistic purposes, I would like to see the authors provide a more in-depth analysis of these injuries.</p> <p>The injury rate was approximately the same for all organs (24-27%) but the discard rate for pancreas was much higher than the others. Can this be explained in more detail?</p> <p>How many patients had more than one organ injured per procurement (i.e. both liver and kidney injured in the same case)? This is not explained. If any existed, when did these cases occur?</p> <p>Were injuries resulting in discarding of the organs more likely to occur at night? When did they occur? If there is room, it might be helpful to include a graph showing when these 12 organs were injured.</p> <p>Although daytime procurements yielded the lowest injury rate, only about 22% of procurements occurred in this time period when it should be 37.5% occurring in this period if one assumes equal distribution throughout the day. What is the peak time of procurement, and can any conclusions be drawn about this and the injury rate at that time?</p> <p>Procurement operations are unique in that they must precede the transplant surgery by 6-12 hours. Procurements done at night result in transplants done the following day. Procurements done in the daytime result in transplants done at night and the wee hours of the morning. The authors note that solid organ transplants done at night have suboptimal outcomes. I think this would make an interesting conundrum for the authors to comment on in the discussion.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Chris Callaghan

Institution and Country: Consultant Transplant Surgeon, Guy's Hospital, London, UK

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below:

This interesting study addresses the important issue of a possible association between time of organ procurement surgery and procurement-related injuries. This is a topic of considerable interest to surgeons and patients, and health administrators. The study is generally well written, and clear, and the conclusions are balanced and based on the findings of the study.

The authors should consider the following:

- 1) The study was performed over a relatively short time period (just 18 months), and almost 5 years ago. Can the authors comment on why they didn't utilise a longer study period (which presumably would result in more damage events, and better statistical power)?

We have chosen to test our hypothesis in a cross-checked, complete database¹. Despite the limited time period the sample size was sufficient to provide statistically significant results. As the reviewers points out correctly, the current data offers ground for more rigorous follow-up studies. These will provide a larger sample size and enables a more detailed analysis.

2) Can the authors comment on the surgical experience of the procuring surgeon? Can they be confident that procurements performed during the day weren't performed by more experienced surgeons? If a procurement was performed in a large academic transplant centre during the day, it might be possible that a more senior surgeon might be involved.

We agree with the reviewer that surgical experience is an important factor in procurement surgery. For this reason, all procurement surgeons in The Netherlands undergo a thorough and intensely monitored training programme. This programme includes the ESOT procurement e-course, a minimum of ten multi-organ procurement procedures followed by an examination by a non-regional procurement surgeon. The certified surgeons are then members of the regional dedicated procurement teams that operate on a 24h basis. This means that the same surgeons perform procurements during the day and during the evening/night-time. This has been added to the Discussion (page 12).

Were the procuring surgeons all on-call for 24 hours? More information on the rota of these surgeons and how this might affect the findings would be useful.

Procurement surgeons serve on a 24-hour basis. When on call, they are not involved in the transplantation rota or any other clinical activities.

3) The authors state that the implanting centres' opinions on the forms took precedence if there was variance between the procuring and implanting teams. Often the organs will be procured and implanted by members from the same transplant unit; sometimes the organs will be exported to another team. Could this introduce bias - e.g. exported organs might be more likely to be coded as damaged if they came from other teams? Is the proportion of exported organs the same for day and nighttime procurements?

The reviewer points out an interesting argument. If present, it would affect the injury rate in both the day as evening-night time group equally. Although this potential bias would be of a limited (statistical) significance it cannot be completely excluded. Therefore, a comment was added to the discussion to address this (Discussion, page 13).

4) There are multiple other papers that look at risk factors for procurement-related injuries that have not been referenced, including:

- Kidney damage during organ recovery in donation after circulatory death donors: data from UK National Transplant Database. Ausania F, White SA, Pocock P, Manas DM. Am J Transplant. 2012 Apr;12(4):932-6.

- Liver damage during organ donor procurement in donation after circulatory death compared with donation after brain death. Ausania F, White SA, Coates R, Hulme W, Manas DM. Br J Surg. 2013 Feb;100(3):381-6.

- A registry analysis of damage to the deceased donor pancreas during procurement. Ausania F, Drage M, Manas D, Callaghan CJ. Am J Transplant. 2015 Nov;15(11):2955-62.

These references have been added with a comment to the manuscript (Methods, page 7; Discussion, page 13).

These papers should be appropriately referenced. In addition, the risk factors for organ damage identified in these papers (e.g. presence of aberrant anatomy) should be taken into account. The authors state that this should be evenly distributed across day/night procurements, but this should be checked and corrected for.

Because donor characteristics (in general) do not affect the timing of procedures, one can assume, that no significant differences exist between both groups on an epidemiological basis. To verify this assumption, we have analysed the distribution of normal and aberrant vascular anatomy in day and evening-night time groups.

Organs that were procured in daytime had an aberrant anatomy in 32 out of 129 organs (25%) as compared to 129 out of 459 (28%) organs that were procured in evening- and night time (p=0.458). These results and a comment on the definition of 'normal' anatomy have been added to the manuscript (Methods; page 7; Results, page 10).

5) How can the authors exclude organ damage from trauma that occurred prior to procurement in their analysis, e.g. motor vehicle accidents?

The quality forms provide the opportunity to indicate whether injury was not related to the procurement procedure. This enabled us to distinct between the aetiology of the injuries.

A more minor point:

6) Page 12 of 25, line 13. This sentence refers to the start time of surgery, though some readers may not note that the definition used is time of aortic cross-clamp. It would be useful to state this clearly in this sentence.

Although the page numbering may be a little different due to the lay-out (Page 12 of 25, line 13) we have addressed this in the manuscript (Methods, page 7).

Reviewer: 2

Reviewer Name: Paul Chestovich

Institution and Country: UNLV School of Medicine, Las Vegas, NV

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

The authors have done a nice study investigating surgical damage occurring during abdominal organ procurement as it relates to the time of procurement. This is a very simple and nicely done study. My comments and questions are below.

Context of using “on one hand” and “on the other” is incorrect. This would probably be better phrased as follows. “It is difficult to relate a specific surgical injury to a particular negative outcome in a patient, because not all intra-operative injuries are noticed and negative outcomes are multifactorial and complex.

Final sentence of introduction, “relationship” instead of “relation” would be more appropriate.

We thank the reviewer for the comments and we have adjusted the manuscript accordingly.

While it can be assumed that vascular anatomy should be equal across the patient distribution, anomalies and clusters of abnormalities can still exist. I suspect that the information on any vascular abnormalities or other factors impacting the operation should exist on the quality forms. It would be helpful if this data were included, should it be available, and actually show that the vascular abnormalities are the same in each group.

The only confounders analyzed are age, height, weight, BMI, sex and donor type. There are other confounders which might make procurement more difficult (i.e. previous surgery leading to adhesions).

A similar remark on vascular abnormalities has been made by the other reviewer. We feel that, on an epidemiological basis, one can assume that no significant differences exist between both groups because donor characteristics do not affect the timing of procedures. To verify this assumption, we have analysed the distribution of normal and aberrant vascular anatomy in day and evening-night time groups.

Organs that were procured in daytime had an aberrant anatomy in 32 out of 129 organs (25%) as compared to 129 out of 462 (28%) organs that were procured in evening- and night time ($p=0.458$). These results and a comment on the definition of ‘normal’ anatomy have been added to the manuscript (Methods, page 7; Results, page 10). Previous abdominal surgery as a possible confounder has been mentioned in the manuscript (Discussion, page 13).

While treating surgical injury as a binary outcome (yes/no) is ideal for simplistic purposes, I would like to see the authors provide a more in-depth analysis of these injuries.

Such an analysis would be relevant for outcome analysis regarding transplant surgery. In this study, we aim to focus on the performance of the surgeon. The size of the current dataset limits subset analysis of the injuries other than critical and non-critical. It would be interesting to see if a more detailed analysis will be possible in the future studies.

The injury rate was approximately the same for all organs (24-27%) but the discard rate for pancreas was much higher than the others. Can this be explained in more detail?

The pancreas is a very delicate organ and minor injuries to the organ can easily result in major complications in the recipient. Organ with minor injuries, possibly acceptable for other organs such as a capsula tear, might therefore lead to discarding of the organ.

How many patients had more than one organ injured per procurement (i.e. both liver and kidney injured in the same case)? This is not explained. If any existed, when did these cases occur?

591 organs were procured from 313 donors and 148 injuries were registered. More than one injury was observed in 20 donors. We have adjusted our analysis for donors with several injured organs with sandwich estimators of the standard errors. This is described in the Methods section (last paragraph, page 8).

Were injuries resulting in discarding of the organs more likely to occur at night? When did they occur? If there is room, it might be helpful to include a graph showing when these 12 organs were injured.

Thank you for the helpful suggestion, 7/12 of the injured organs that were discarded were procured during evening/night-time. It has been added in the manuscript (Results, page 11) and can now be found in supplementary table 2.

Although daytime procurements yielded the lowest injury rate, only about 22% of procurements occurred in this time period when it should be 37.5% occurring in this period if one assumes equal distribution throughout the day. What is the peak time of procurement, and can any conclusions be drawn about this and the injury rate at that time?

Please refer to the newly added supplementary figure 1, indicating the number of procedures over 24 hours. Most organs were procured in procedures starting between 00:00-01:00. In the daytime group, the number of procurements per hour was somewhat stable throughout the period. In the evening/night-time group, a normal distribution can be observed in the number of procurements per hour (median around 12AM). No clear conclusions can be drawn based on these findings in our opinion.

Procurement operations are unique in that they must precede the transplant surgery by 6-12 hours. Procurements done at night result in transplants done the following day. Procurements done in the daytime result in transplants done at night and the wee hours of the morning. The authors note that solid organ transplants done at night have suboptimal outcomes. I think this would make an interesting conundrum for the authors to comment on in the discussion.

In the Netherlands, the planning of the procurement procedure is mainly dependent upon the availability of operating facilities in the local donor hospitals rather than to the planning of the transplantation. In the current manuscript we have not commented on the outcome of nightly transplant procedures as there is a lack of evidence of increased complication rates.

Theoretically, the mechanism of 'fit to perform' is of equal importance to procurements and transplantations. Therefore, best solution would be to perform the procurement in the early morning and the transplantation in the (early) afternoon. A comment has been added to the manuscript (Discussion; page 15).

VERSION 2 – REVIEW

REVIEWER	Chris Callaghan Guy's Hospital, London UK
REVIEW RETURNED	14-Jun-2018
GENERAL COMMENTS	I have satisfied that the authors have adequately addressed the issues I raised in my initial review.