Bias in Before–After Studies: Narrative Overview for Anesthesiologists

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Before–after study designs are effective research tools and in some cases, have changed practice. These designs, however, are inherently susceptible to bias (ie, systematic errors) that are sometimes subtle but can invalidate their conclusions. This overview provides examples of before–after studies relevant to anesthesiologists to illustrate potential sources of bias, including selection/assignment, history, regression to the mean, test–retest, maturation, observer, retrospective, Hawthorne, instrumentation, attrition, and reporting/publication bias. Mitigating strategies include using a control group, blinding, matching before and after cohorts, minimizing the time lag between cohorts, using prospective data collection with consistent measuring/reporting criteria, time series data collection, and/or alternative study designs, when possible. Improved reporting with enforcement of the Enhancing Quality and Transparency of Health Research (EQUATOR) checklists will serve to increase transparency and aid in interpretation. By highlighting the potential types of bias and strategies to improve transparency and mitigate flaws, this overview aims to better equip anesthesiologists in designing and/or critically appraising before–after studies. (Anest Analg 2017;XXX:00–00)

Alternative study designs to randomized controlled trials (RCTs) are common in clinical research. The before–after design uses a quasi-experimental approach that compares outcomes after an intervention/event with outcomes from before the intervention/event. In addition to “before–after,” such designs are cited in the literature as “pre-post,” “quasi-experimental,” “controlled before after,” and “observational” studies. Data can be collected prospectively or retrospectively. The “after” cohort can be the same as the “before” cohort (within-subjects design), or it can be different (Figure 1). Such studies are typically uncontrolled, although occasionally control group(s) (eg, from within the same institution, a nonparticipating hospital/city/state with similar demographics) may be used. However, even when a control group is used, there is typically no randomization. Before–after studies are useful in assessing the impact of new health services, assessment tools, safety initiatives, guidelines, and educational programs, etc, and in exploring new concepts and generating hypotheses. Some before–after studies have initiated major changes in anesthesia practice. The link between etomidate sedation and poor outcomes in intensive care unit (ICU) patients1 and between surgical safety checklists (SSCs) and improved outcomes2 are good examples.

Due to its relative simplicity, circumvention of ethical issues, low-resource requirements, and associated costs, the before–after design is common in the perioperative literature. It is therefore important that anesthesiologists be aware of the types of bias that may lead to their inappropriate planning, execution, and/or interpretation. We herein provide a brief qualitative review of anesthesia-related before–after studies to demonstrate different types of potential bias. We also discuss ways in which bias could have been minimized and/or methods for increasing its transparency so that anesthesiologists are better equipped to subsequently design and/or interpret such studies.

METHODS

A series of literature searches in the Medline, Embase, and CINAHL databases using a combination of keywords and subject headings were conducted by a Health Sciences Librarian (S.W.), and relevant references were retrieved. The representative Medline search strategy is presented in Figure 2.

The references cited in the current manuscript emanated from a combination of the above-mentioned literature searches, previous readings of the authors, the peer review process itself, and/or references cited within these manuscripts. All references are indexed on Medline, Embase, CINAHL, Web of Science, and/or Google Scholar. We confined our final selection of articles to those that could illustrate the points being made and that had relevance to anesthesiologists. The authors vetted the articles and unanimously agreed on the choices made. This is not a guide to all potential sources of bias but rather a selective overview of types of bias common in before–after studies because of their design. Although this review addresses sources of bias (and mitigating strategies) in traditional analyses of before–after data, it does not address potential techniques that investigators might use to model phenomena such as endogenous effects embedded within dynamical systems. Anesthesia-related examples of such dynamical systems include the impact of time of day, day
of week, holidays, and/or the time of year on surgical demand or the effects of geographical, socioeconomic, and/or ethnic background on labor durations. Given that this is a selective overview of studies to illustrate different types of bias (as opposed to a comprehensive systematic or scoping review), an EQUATOR reporting checklist is not applicable to this work.

Bias is a form of systematic error that can be introduced during study design, execution, data collection, analysis, reporting, and/or publication. Unlike random error that results from sampling error, bias is independent of sample size and statistical significance. To restate, even if before–after studies are enormous with a high magnitude of statistical significance, the presence of bias can completely invalidate the conclusions. Because of their design, before–after studies are inherently susceptible to many types of bias.

**Selection/Assignment Bias**

Selection/assignment bias is when the sample under investigation has a different composition with regard to etiological factors than the population it is intended to represent. Specific to before–after study designs, it is when the subjects/groups being assigned/compared in the before and after cohorts are not equal for reasons other than the intervention of interest. The causes may be subtle. For example, Radwan et al instituted a new massive transfusion (MT) protocol consisting of stocking prethawed plasma for prompt administration to exsanguinating trauma patients. Data for patients receiving plasma during the first few hours were compared retrospectively from before versus after the institution of the MT protocol. They found that the before cohort had significantly lesser injuries than the after cohort that rendered the comparison invalid. In the before protocol era, without the availability of prethawed plasma, plasma administration was delayed. As a result, the most severely injured patients died before receiving the first unit of plasma and were therefore never included in the study. Conversely, in the after cohort, patients (including the sickest ones) were quickly transfused and included in the study. This also serves as an example of survivor bias. In both the before and after periods, MT was defined as ≥10 units of packed red blood cells (PRBC). But because the more seriously injured patients died before receiving ≥10 units of PRBC in the before cohort, they would not have been included, whereas those with serious injuries who benefitted from early plasma and platelets survived long enough for ≥10 units of PRBC and inclusion in the study.

**History Bias**

By definition, before–after data are collected from 2 different time periods. History bias occurs when researchers fail to consider relevant events or changes that precede an intervention or cooccur while it is in progress to affect the outcome. The rate at which medical practices, environments, and/or study populations change is inevitably highly variable, and the impact of such changes would be specific to the before–after study. As a result, it is not possible to define an optimal or maximal acceptable time separation between the before and after periods. However, it may be safe to assume the shorter, the better, to reduce the likelihood that other changes are occurring during this time period so long as there is a clear division (no carry-over effect) in the nonexposure and exposure to the intervention/event in the before versus after cohorts.

As an example of history bias, Bowton et al compared the incidence of ventilator-associated pneumonia (VAP) before versus after implementing hospital-wide use of tapered-cuff endotracheal tube and found that there was no reduction. However, they also found that adherence to other VAP-prevention measures had waned in the after period, making it difficult to determine whether the tapered-cuff endotracheal tube per se did in fact have any impact on VAP rates.

Another example of history bias can be seen in studies on medical emergency teams (METs), the purpose of which are to intervene in prearrest situations. In response to before–after studies that demonstrated a reduction in mortality after the implementation of METs, some hospitals established around-the-clock in-hospital METs. However, Joffe et al
reviewed mortality data from a Canadian university hospital in which no METs had been established and found similar decreases in mortality. Likewise, no reduction in mortality was observed during the time periods that corresponded to those of studies reporting no change14–16 (ie, alterations in mortality rates were likely occurring for reasons other than MET implementation). A cluster RCT (see below) confirmed the finding that MET implementation did not affect the incidence of cardiac arrest, ICU admissions, or unexpected death.17

Regression to the Mean
Regression to the mean is a statistical phenomenon whereby extreme outliers (whether high or low) in clinical data tend to become less extreme with repeated measurements and this is present whenever there is an intrasubject variation on a repeated test.18 For example, Browne et al19 administered psychometric tests to cardiac surgery patients preoperatively, at discharge, and then 3 months postoperatively. By analyzing the data with preoperative scores categorized into low, medium, or high cognitive function, these authors showed that those with the highest preoperative scores were disproportionately more likely to show cognitive decline after surgery whereas those with low baseline performance had a tendency toward improvement. If an interim intervention had been instituted in response to the extreme data, it might have been concluded that the intervention was successful.

Test/Retest Performance Bias or Repeat Testing Bias
In a pretest–posttest situation, subjects tend to remember some of the questions and may remove errors in the posttest so that they appear to do better (even) without the effect of the intervention.20 This may occur during within-subjects study designs when the outcomes are performance based. In healthy volunteers, Bartels et al21 demonstrated that practice effects for cognitive function tests are pronounced in the early phases of high-frequency testing. Since the same test or same type of test is used in the pre- and postoperative periods in postoperative cognitive dysfunction research, it is possible that learning may affect all postoperative test results. The timing and frequency of test administration may have implications for all studies of short- and long-term repetitive neuropsychological testing.
Maturation Bias
Maturation bias occurs as a result of biological or psychological changes occurring within subjects, and these changes may account in part, or in total, for the effects observed in the study.22 For example, Knipp et al23 examined cognitive function in 39 cardiac surgery patients preoperatively, on hospital discharge, 3 months, and then again at 3 years postoperatively. These authors observed a decline in cognitive function 3 years postoperatively. However, given that there was no control group, it is possible (even likely) that the observed cognitive decline was due to natural aging rather than the cardiac surgery performed 3 years earlier.

As a hypothetical example of bias from natural processes, children with benign chronic pain are given a vitamin pill every day. At the 12- and 24-month follow-ups, 52% and 70%, respectively, have no more pain,24 giving the false impression that vitamin supplementation is effective. However, a control group without the pill may have shown the same improvement.

Observer/Interviewer Bias
Observer/interviewer bias occurs when the researchers participating in outcome assessments, data collection, and/or interpretation are not blinded to the purpose of the study and/or the intervention of interest. This occurs when outcome assessments are systematically influenced by the assessors’ conscious or unconscious predispositions.25 Because most before–after studies lack a control group and blinding, the researcher’s bias may influence the study outcomes. A before–after study conducted by Larsen et al may potentially have been affected by observer bias despite stating that “health care staff in the pre and postoperative periods were unaware of the ongoing study.” This before–after study was designed to confirm the results of a RCT (previously conducted by the same senior investigator) that demonstrated the efficacy of an accelerated perioperative care and rehabilitation program for total hip arthroplasty patients.26 Because this prospective before–after study was conducted under the same leadership with the orthopedic surgeons and physiotherapists as coinvestigators, it is likely that health care providers assessing, recording, or interpreting patient outcomes were not adequately blinded to the purpose of the study. Since the whole purpose was to confirm the efficacy of the accelerated recovery protocol previously demonstrated in their RCT, it is likely (even if at the subconscious level) that health care provider/observer knowledge may have affected the study outcomes.

Retrospective Bias
Humans have an innate ability to discern patterns in random noise.27 Because investigations are often initiated by an investigator’s observation of patterns or unexpected associations in their patients, it is not surprising that conducting a retrospective analysis of a pattern already observed would yield statistically significant results.27 Although retrospective reviews can lead to breakthroughs, many are just patterns in random noise.27 An elegant example of this phenomenon is Greenberg et al’s observation of increased rainfall during the Society of Pediatric Anesthesia annual meetings held at different locations around the United States. While the statistical analyses are very strong, the association can be attributed entirely to random patterns.

In terms of an anesthesia-related example, the examination of the impact of a prethawed plasma program on major trauma resuscitations (discussed previously) by Radwan et al used retrospectively collected data for the before and after cohorts. It is conceivable that the authors, having formed the impression that exsanguinating patients given plasma early had improved survival, went on to retrospectively review data before and after introduction of a thawed plasma trauma program. Not surprisingly, their finding that a thawed plasma program saves lives went on to confirm their observation, which might have been true or simply random noise. Indeed, although early plasma administration in severe trauma is now common practice, it remains an unproven concept with many detractors.29

Similarly, for the heavily cited example by Watt and Ledingham in which etomidate was associated with poorer outcomes in ICU patients, the data were collected retrospectively in the before and after periods that make it impossible to determine whether those patients who received etomidate were already at a greater risk of mortality than the before group that did not receive etomidate or whether the observation was just due to random noise. To date, the association between etomidate sedation and ICU patient outcomes remains unproven.

The Hawthorne Effect
The Hawthorne effect can occur when a subject knows they are being observed and this awareness can change their behaviors to affect the outcome(s) of interest.6 For example, when hand washing by hospital staff was observed after a training program, the group overtly observed had a much higher compliance rate than the group covertly observed.31 Usichenko et al reported improvements in patients’ pain, nausea, vomiting, and fatigue after surgery with the implementation of a quality management system but acknowledged that there might have been a Hawthorne effect due to increased vigilance by anesthesiologists. The Hawthorne effect can affect patients as well. De Amici et al demonstrated that mere awareness of being in a study could positively impact patients’ sense of pain and well-being during the postoperative period.

Instrumentation/Measurement Bias
Instrumentation/measurement bias is present if the outcome measurements are imprecise due to instrument miscalibration, the measurement procedure itself, or the human investigator.34 In this context, it would be because of differences in the measures in the before and after cohorts. Chapman et al35 compared the risk of transfusion-related acute lung injury (TRALI) from plasma before and after institution of a male-only plasma program in the United Kingdom in late 2003 and found that the incidence of TRALI from plasma or platelet transfusion had dropped from 16 in 2003 to 1 in 2006. However, in 2006, the definition of TRALI was changed from onset of dyspnea, hypoxia, and lung infiltrates within 24 hours of transfusion to within 6 hours of transfusion. It is possible that some of the benefits documented had been exaggerated because TRALI had been overdiagnosed in the before cohort and/or underdiagnosed in the after cohort.

A similar situation occurred when Wehrli et al conducted cost analyses after the implementation of a thawed plasma program and determined that it reduced plasma wastage and
associated costs. In actual fact, 1 reason why they observed reduced plasma waste was because simultaneous with launching the program, these authors also extended the shelf life of all thawed plasma at −6°C from 24 hours to 6 days.

Attrition Bias/Loss to Follow-Up/Survivor Bias
Attrition/loss to follow-up occurs when there is differential nonresponse in one group compared to another.29 In this context, it would be where patients in the before phase are unavailable in the after phase. Attrition may be due to death, illness, people moving away, interventions being too difficult, too inconvenient, etc. The potential bias from this phenomenon was demonstrated in a study by Kat et al37 that examined postoperative delirium, a known risk factor for long-term mortality and morbidity. They observed that 54.9% of hip surgery patients who had developed delirium postoperatively had died compared to 34.1% of those who did not.37 In addition, half of the patients with delirium were institutionalized at follow-up compared to only 28.6% of those without delirium.37 As a result, any psychometric testing at 30 months after the hip surgery would likely result in a disproportionate number of relatively well patients taking the tests. If all postoperative patients were tested before an intervention and the results compared with that obtained from a similar test taken by only those available at the 30-month follow-up, it might appear as though the surgery had improved brain function.

Likewise, Knipp et al23 monitored cognitive function preoperatively and at 3 years after aortocoronary bypass surgery and determined that several cognitive function domains had declined. However, of the 39 patients who completed the preoperative assessments, only 60% were available for follow-up at 3 years. It is possible that the remaining 40% were too unwell to participate, or alternatively, they were doing so well they considered the follow-up unnecessary. Such attrition makes it difficult to draw meaningful conclusions.

WAYS TO IMPROVE THE BEFORE–AFTER DESIGN AND ALTERNATIVES
Assuming that a RCT is not feasible, one may be able to reduce the bias in before–after studies by using a number of strategies.

Accounting for Factors That Could Influence Outcome
To minimize history threat, all changes that could influence the outcomes should be accounted for, and the before and after groups should be well matched. However, since some covariates may not be known or controllable, the time span between the 2 cohorts should be minimized to reduce the effects of trends. In the study by Haynes et al3 cited previously that demonstrated a significant reduction in complication rates after the implementation of a SSC, the before and after cohorts (each <3 months) were in close succession.

Control Group
A control group may be added to the “before” and/or “after” periods. If this control group is randomly assigned, the trial becomes a pseudo-RCT that may lessen the risk of unrecognized temporal trends. Diffusion of knowledge may prevent the establishment of a true control, especially if it is within the same institution. For example, it would simply be impractical for Haynes et al2 to have clinicians perform the SSC on only half the patients within the same institution. However, if the control and study groups are well matched, one can assume that they are influenced by the same underlying trends. Nevertheless, without randomization, the results must be interpreted with caution. Another approach is to compare to national trends. For example, Haynes et al2 claimed that the improvements in their after cohort were not seen in national trends.

Statistical Considerations in Study Design and Analysis
Statistical issues encountered during peer review of anesthesia manuscripts have been nicely summarized,38 and many of these may be applicable to before–after study designs. When a study involves repeated measures over time, correlations between successive measures must be taken into consideration and the statistical model explained clearly so the reader can understand not only the rationale for using the model but also its associated assumptions.38 Similarly, the process of batching the data related to probability distributions and the effect of trends such as season of year, day of week, or time of day should be accounted for (F. Dexter, Department of Anesthesia, University of Iowa, personal communication, 2017). Another issue may occur when the study has a dependent variable that may differ among providers (ie, physicians) but the dependent variable is not analyzed by stratification or mixed models. As an example, Mannarots et al29 conducted a prospective before–after study looking at implementation of an enhanced recovery after bariatric surgery protocol and found that it led to quicker procedure times, reduced length of in-hospital stay, and increased complication rates. However, a major confounder not accounted for was the surgeons and/or the bariatric surgical care team in the before versus after periods. The outcomes should have been analyzed by stratification or mixed models.38 Given that potential confounders were unaccounted for, the conclusion that “by implementing an enhanced recovery after bariatric surgery protocol, you can achieve efficient and safe bariatric care, as well as a substantial reduction in operation time, hospital length of stay, and costs” may not be appropriate. While statistical mitigation strategies of bias are outside the scope of the current review, a statistical tutorial on bias is available.40

Time Series
A time series is literally a set of measures on a variable (or variables) taken over time.41 In this context, it is collecting a set of measures before the intervention for comparison with a set of measures taken after the intervention of interest. Data are collected at multiple and evenly spaced time points before and after the intervention. If the improvement in the primary outcome measures is not above temporal trends, no improvement can be attributed to the intervention or event. Twenty data points before and 20 after the intervention/event have been suggested as required to allow full-time series modeling to be used.41

Alternate Study Designs
When conventional RCTs are not feasible, alternative designs include parallel or stepped wedge cluster RCTs that
involve randomization of groups of individuals (clusters) to receive an intervention42 (see Figure 3 for an illustration of a conventional parallel cluster and a stepped wedge RCT). A group of centers contribute data for the before cohort, and at predefined time points, the clusters are switched to the intervention group in a random order and stay there until the end of the study. All participants eventually receive the intervention, which can avoid ethical issues that may arise from withholding a treatment or intervention. As mentioned previously, Hillman et al17 used a cluster RCT to demonstrate that METs do not affect outcomes. Haugen et al43 used a stepped wedge clustered RCT design to study the effect of having a SSC, sequentially rolling out in a random order until 5 surgical clusters had received the SSC. They found that implementation of SSC was associated with reduction in morbidity, length of in-hospital stay, and mortality. As another example, Dainty et al44 used this methodology to evaluate a knowledge translation strategy to increase the utilization rate of induced hypothermia in cardiac arrest survivors in 37 Canadian hospitals. They randomly assigned participating hospitals to receive the knowledge translation strategy according to a sequential rollout over a number of time periods. The difficulties of delivering the intervention to all hospitals simultaneously and the opportunities for modeling the effect of time on the effectiveness of the intervention made the stepped wedge design desirable. In addition, stepped wedge cluster RCTs provide a method of obtaining a control group in situations where it would otherwise be impractical. Such designs also allow one to control for the diffusion of knowledge or for other unmeasured confounds.

Empirical Bayes

Another method called empirical Bayes has been applied to roadway safety research for over 20 years. This method is beneficial in that it can control for regression to the mean as well as other changes not due to the intervention. This is achieved by calculating the parameters of interest before the intervention based not just on the participating population but instead on the weighted average of the participating population plus similar nonparticipating populations.45 However, the complexity of this method requires highly trained and experienced analysts and the data can be very extensive, which can make resource requirements prohibitive.45

Mitigating the Hawthorne Effect

If possible, the situation in which data on the before cohort are collected retrospectively while data on the after cohort prospectively should be avoided, as only the latter may benefit from a Hawthorne effect. In addition, this would undoubtedly result in the situation where data are missing in the before cohort. In the study by Haynes et al2, both group data were prospective.

During observation and evaluation of behavior, being discrete may reduce the Hawthorne effect. Rampersad et al46 used a video camera instead of a person to observe behaviors after an anesthesia quality improvement initiative to reduce line sepsis. However, many anesthesiologists in their study were aware that they were being filmed. Covert observers or videotaping of behavior may reduce the bias,46 but this may raise ethical issues.

Studies that do not involve direct observation of behavior may be less susceptible to this bias. For example, comparing

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**Figure 3.** Illustration of the conventional parallel cluster (A) and the stepped wedge (B) cluster randomized designs. In the parallel design, each cluster has a 50% chance of being exposed to the intervention of interest from the beginning. The remaining 50% is not exposed during the study. In this example, clusters 1, 4, 6, and 8 are randomized to receive intervention. In the stepped wedge design, all 8 clusters are not exposed to the intervention as the “before” data are collected. In phase 2, a randomly selected cluster is exposed. In phase 3, another randomly selected cluster is exposed, and so on. Here, the order at which the clusters are randomized to transition to intervention is 2, 1, 8, 6, 7, 4, 3, and 5.
board examination results after implementation of competency-based residency training may contain multiple confounders but not Hawthorne effects.

It is useful to take a longer view to see if improvement after an intervention/event is sustained, as real change may not be evident when the Hawthorne effect is no longer present. For example, Cartier et al. measured the effectiveness of simulation-based training of anesthesia residents in improving short- and long-term competency in, and knowledge of, central venous catheter insertion by comparing assessment immediately before and after and also 34 weeks later. They found that performance was superior immediately after training and although less so on average 34 weeks later, the long-term improvement was still statistically significant. However, because of the lack of a control group, it is difficult to separate the effect of the simulation-based training and the effect of accumulation of experience as would be expected over time (history and maturation bias).

Consistency in Measuring or Reporting Criteria
In the TRALI example (Chapman et al.) cited earlier, the bias would have been reduced if the researchers applied the same criteria to the definition of TRALI for both the before and after cohorts. Likewise, if Wehri et al. had not extended the shelf life of thawed plasma from 24 hours to 6 days just as they were conducting the cost analysis, these authors may not have concluded (based on their results) that storing thawed plasma to allow immediate use in emergencies reduces waste with cost-benefits.

Blinding of Assessors
If possible, assessors should be blinded to the purpose of the study and the intervention. In cases in which both the before and after data are collected retrospectively, the assessors should also be blinded to the dates the patient data were recorded. If a control group is present, assessors should not be aware of the patient assignment. Finally, the people applying the intervention should not be the same as those assessing the outcomes.

Reducing Reporting and Publication Bias
Adoption and enforcement of transparent reporting checklists (ie, Strengthening the Reporting of Observational Studies in Epidemiology [STROBE], Standards for Quality Improvement Reporting Excellence [SQUIRE], Transparent Reporting of Evaluations with Nonrandomized Designs [TREND]) for observational quasi-experimental designs by biomedical journals may improve reporting (and thereby, reduce bias). Such improvements have been demonstrated in RCTs with the implementation and enforcement of the Consolidated Standards of Reporting Trials (CONSORT) checklist. Likewise, improvements in medical journal acceptance and publication of negative studies will reduce the occurrence of publication bias.

Concluding Remarks
Because of their relative simplicity, convenience, circumvention of ethical issues, low-resource requirements, and associated costs, before-after study designs will remain common in anesthesia-related research. A thorough understanding of the potential sources of bias inherent to these study designs and ways to mitigate such bias as outlined herein will ensure that anesthesiologists are better equipped to design and/or interpret such research investigations.

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