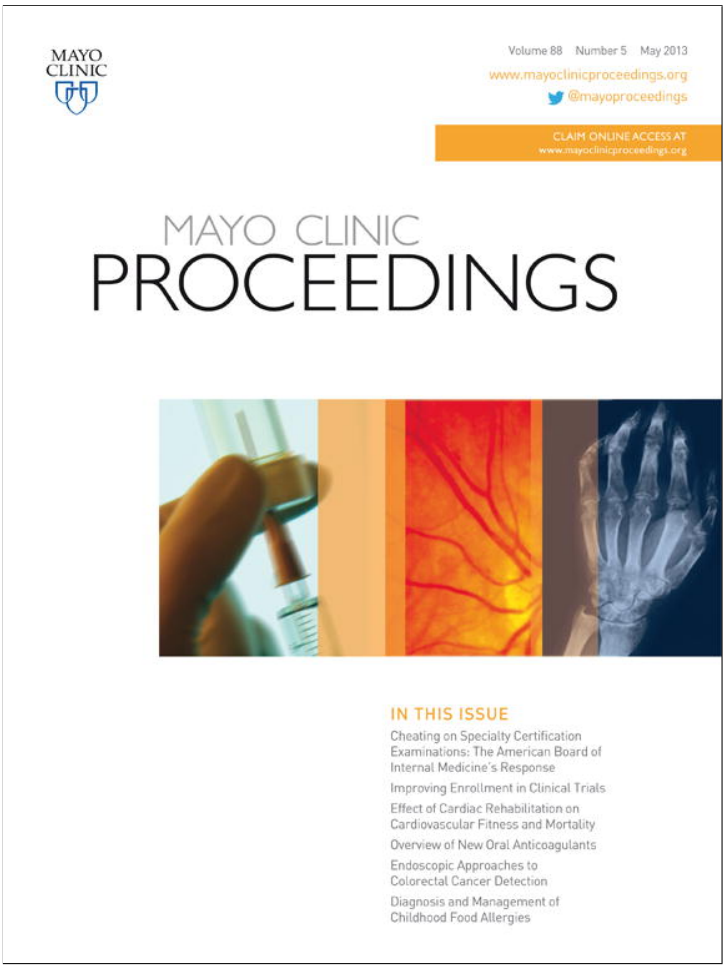

ORIGINAL ARTICLE

MAYO CLINIC

Protocol Understanding and Anxiety in Perioperative Clinical Trial Patients Approached for Consent on the Day of Surgery

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Abstract

Objective: To determine whether approaching patients for consent on the day of surgery impairs understanding or produces unacceptable anxiety compared with obtaining consent before the day of surgery.

Patients and Methods: We assessed the effect of the timing of obtaining consent for a moderate- to high-risk factorial trial of clonidine and aspirin in patients having noncardiac surgery. Between February 1, 2011, and November 31, 2011, 2 study personnel used the same standardized script to recruit patients before the day of surgery or on the day of surgery. Patients eligible for the trial were preferentially approached to obtain consent before the day of surgery in the preoperative clinic. Patients who did not attend the preoperative clinic or could not be approached that day were approached for consent on the day of surgery. We evaluated anxiety before and after the trial was discussed, protocol knowledge, consent rates, and perceived obligation to participate. All comparisons were adjusted for differences in potentially confounding variables using inverse propensity score weighting.

Results: Patients approached on the day of surgery compared with before the day of surgery had noninferior understanding of the comprehension score (adjusted mean difference, −0.19; 90% CI, −0.47 to 0.10; $P<.001$ for noninferiority) and a noninferior mean increase in the postapproach anxiety score (adjusted mean difference, 0.19; 90% CI, −0.29 to 0.68; $P=.003$ for noninferiority). Perceived obligation to participate was not greater on the day of surgery (adjusted mean difference, 0.09; 95% CI, −0.21 to 0.40; $P=.57$ for superiority); however, consent rates were significantly lower (31% vs 59%; odds ratio, 0.49; 90% CI, 0.33 to 0.72; $P=.46$ for noninferiority).

Conclusion: Approaching patients to obtain consent to participate in a perioperative interventional trial on the day of surgery does not compromise essential elements of the consent process.

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For editorial comment, see page 428

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The ethical basis for human participation in clinical research is detailed in the Belmont Report, which cites autonomy, beneficence, and justice as basic ethical tenets in research.[1] Autonomy, in particular, refers to the primacy of the patients' choices in determining the overarching course of their medical care, including their participation in research. To comply with this ethical principle, patients' decisions to participate in research must be on the basis of full understanding of potential risks and benefits of the proposed study. Thus, the ability of patients to comprehend the purpose and implications of research that they may be involved in is crucial to conducing ethical research.

Potential research participants generally obtain most information regarding studies from an investigator or study personnel who present an explanation of the proposed study, including its goals, interventions, risks, and potential benefits. Patients are also given a copy of the consent form. One factor that might influence patients' understanding, as well as willingness to consent, is the timing of the consenting process. Discussing research with potential participants is generally not stressful,[2] but patients approached shortly before surgery might understandably already be sufficiently stressed by their anticipated procedures to compromise their ability to adequately acquire and process information about a presented study.

In the absence of compelling evidence, institutional review boards (IRBs) have developed discrepant policies regarding when they will allow trial consent to occur before surgery. For example, some IRBs do not allow consenting on the day of surgery, whereas others allow study personnel to obtain consent for trial participation on the day of surgery.

Restricting day-of-surgery consenting can seriously limit the feasibility of certain types of research. Because most patients undergoing surgery are admitted on the day of surgery,[3] it has become increasingly difficult for anesthesiologists and other nonsurgeon investigators to approach patients a day or more before surgery. Consequences of restricting day-of-surgery consent for research include the following: (1) many patients are never offered the opportunity to participate in research, despite the fact that many of them are potentially interested and might wish to participate if approached; (2) the cost of identifying and consenting patients can become high enough to preclude minimally funded, investigator-initiated research, a critical and often the most creative part of the clinical research continuum; and (3) physicians are forced to make practice decisions based on suboptimal data because perioperative trials are not undertaken.

We undertook a prospective, observational study to ascertain the effects of day-of-surgery consenting. Our primary joint hypothesis was that consent on the day of surgery compared with consent before the day of surgery for a perioperative interventional trial (Perioperative Ischemic Evaluation 2 [POISE-2]) would indicate the following: (1) noninferiority (ie, not worse) for understanding of trial procedures and risks and (2) noninferiority (ie, not worse) for incremental anxiety increase after the consenting process. We thus deemed it acceptable to acquire consent from patients on the day of surgery as a whole only if those patients understood the consent as well as patients who consented before that time *and* their incremental anxiety levels were not worse as a result of consenting on the day of surgery. Our secondary hypothesis was that patients approached on the day of surgery give consent at a similar rate and do not feel more compelled to participate compared with patients who consent before the day of surgery.

METHODS

This study was conducted as a substudy of the POISE-2 trial, a perioperative, interventional trial. POISE-2 is an international trial that is primarily funded by the Canadian Institutes of Health Research. It has already randomized more than 7000 of 10,000 patients in approximately 130 centers. The Cleveland Clinic, the site of this consent substudy, is the lead clinical site within the United States.

The POISE-2 Trial

POISE-2 is a factorial randomized controlled trial evaluating the effect of low-dose aspirin vs placebo and low-dose clonidine vs placebo on the composite of 30-day mortality and nonfatal myocardial infarction. Inclusion criteria for POISE-2 are meant to select patients with, or at risk of, atherosclerotic disease. Specifically, patients must be at least 45 years old and scheduled for noncardiac surgery that requires at least overnight admission to the hospital after surgery. In addition, patients must have a history of coronary artery disease, peripheral vascular disease, or stroke; be undergoing major vascular surgery; or have 3 of 9 risk factors (eg, history of transient ischemic attack). Exclusion criteria included the following: known allergy to aspirin or clonidine, systolic blood pressure less than 105 mm Hg, heart rate less than 55 beats/min, second- or third-degree heart block and no pacemaker, requirement for therapeutic anticoagulation immediately after surgery, or undergoing intracranial surgery, carotid endarterectomy, or retinal surgery.

Consent Substudy Protocol

Most patients with risk factors that qualify them for POISE-2 are evaluated in the Cleveland Clinic preoperative clinic and were approached for consent during these visits between February 1, 2011, and November 31, 2011. However, some patients are evaluated solely in surgical offices or are medically cleared elsewhere and first arrive at the main campus on the day of surgery. Others come through the preoperative clinic but are missed by our consenting team because of conflicting appointments or because their eligibility was not apparent from our electronic records. With IRB approval, these patients were approached on the day of surgery

to participate in POISE-2, and all these patients represent the experimental group. Patients were approached on the day of surgery at least 1 hour before surgery was anticipated. Patients approached for consent in the preoperative clinic days before surgery represent the control group in this substudy. In either setting, patients who did not wish to speak to us were free to decline.

Uniformity between the 2 consenting investigators (A.C. and C.I.) was achieved by jointly developing a script that they memorized. Both individuals had extensive practice working with and consenting for the POISE-2 trial before the start of this substudy. Both consenting investigators also participated in extensive simulation exercises with our regulatory director to further harmonize their approach. Our goal was to provide a reproducible, complete, and professional consenting environment for potential study participants and to minimize the effects of different consenters on the process. The schedule was arranged so that each consenting investigator sought consent from patients in each environment.

Measurements

Patients who agreed to hear about the POISE-2 protocol were initially given the 6-item short-form version of the State Trait Anxiety Inventory (STAI-SF) to assess baseline anxiety. Each item ranges from 1 (minimal anxiety) to 4 (high anxiety) for a total score with possible range of 6 to 24. The STAI-SF is a well-validated instrument that is derived from the full 40-item STAI and maintains similar scores to the full STAI.[4] It is a widely accepted tool for measuring anxiety and has been used in numerous research settings.[5,6]

After obtaining the baseline STAI-SF score, the full POISE-2 protocol was presented, and the number of questions each patient asked was recorded. After the presentation, patients were asked if they wished to participate in POISE-2. Their responses were recorded and used to determine consent rates on the day of surgery and before the day of surgery. All patients, whether or not they agreed to participate in the POISE-2 trial, were then asked to fill out the STAI-SF again for comparison with baseline. Our comprehension instrument was a 6-item questionnaire consisting of closed-ended, multiple-choice questions that were specific to the POISE-2 protocol. Comprehension scores thus had a possible range of 0 (all incorrect) to 6 (all correct). Patients were then asked to describe the extent to which they felt obligated to participate on a 6-point Likert scale (with 0 indicating no obligation and 5 indicating very much obligated; Supplemental Appendix 1 [available online at http://www.mayoclinicproceedings.org]). Patients who agreed to participate in POISE-2 were randomized and treated per the trial protocol.

In addition to routine demographic details, such as age, sex, and race, we recorded the highest level of education achieved by the patients because previous studies indicate that patient literacy and educational level play a role in consent rates and understanding of research protocols,[7] interview duration, and number of questions asked by patients during interview. The STAI-SF for anxiety (lower is better), the questions to assess comprehension, and the Likert scale for perception of obligation (lower is better) are provided in Supplemental Appendix 2 (available online at http://www.mayoclinicproceedings.org). We also collected surgical time and *International Classification of Diseases, Ninth Revision* procedure and diagnosis codes of each patient through the Cleveland Clinic Perioperative Health Documentation System. On the basis of the *International Classification of Diseases, Ninth Revision* codes, we calculated the risk stratification index (RSI) in hospital mortality for each patient.[8]

Statistical Analyses

We adjusted for potential confounding of the relationship of interest using inverse propensity score weighting on potentially confounding variables. A propensity score was first estimated for each patient in a multivariable logistic regression model as the predicted probability of being a day-of-surgery patient as a function of all potentially confounding variables (Table 1). All variables were included in the propensity score model, regardless of statistical significance. We adjusted for confounding in all primary and secondary analyses by weighting each patient with the inverse of its estimated propensity score.[9] Because of the small percentage of missing values (<5% all variables), we used medians to impute missing data of continuous and ordinal variables and randomly assigned yes or no to missing data of binary variables.

TABLE 1. Baseline Characteristics and Surgical Factors by Approached Time[a,b]

Factor	Approached on day of surgery (n=72)	Approached before day of surgery (n=166)	STD	STD after weighting by IPS
Female	39 (54)	58 (35)	0.39	−0.06
Age (y)	69±10	65±11	0.41	0.16
White race vs other	61 (85)	148 (89)	−0.13	0.11
ASA status[c]			−0.16	0.08
2	18 (25)	29 (18)		
3	49 (68)	124 (75)		
4	5 (7)	12 (7)		
BMI[d]	28±6	32±8	−0.55	−0.19
Educational level[e]			0.34	0.11
Some high school	6 (9)	12 (7)		
High-school graduate	16 (24)	60 (37)		
Some college	21 (31)	51 (32)		
Bachelor's degree or higher	24 (36)	38 (24)		
Prior research experience[f]	19 (29)	36 (22)	0.15	−0.08
Able to read consent[g]	19 (27)	19 (12)	0.39	−0.11
Interview duration (min)[h]	20±10	22±8	−0.16	−0.10
No. of questions asked per patient[i]	2 [1 to 3]	3 [2 to 4]	−0.48	0.23
RSI (in-hospital mortality)[c]	−2.5 [−3.0 to −2.2]	−2.7 [−3.3 to −2.2]	0.31	0.37
Length of surgery (h)[c]	3.6 [2.9 to 4.5]	4.3 [3.3 to 5.7]	−0.42	0.14
Interviewer A vs B	38 (53)	41 (25)	0.60	−0.07

[a]ASA = American Society of Anesthesiologists; BMI = body mass index; IPS = inverse propensity score (ie, inverse of the estimated propensity score, which was estimated from a multivariable logistic regression model as the predicted probability of being day of surgery as a function of all factors); RSI = risk stratification index; STD = standardized difference (ie, the difference in means or proportions divided by the pooled SD; a variable with an absolute standardized difference >0.28 is considered imbalanced [$1.96\sqrt{(n_1+n_2)/(n_1n_2)} = 0.28$, where n_1=72 and n_1=166].[10]

[b]Data are presented as No. (percentage), mean ± SD, or median [interquartile range].

[c]Missing 1 data point.

[d]Missing 6 data point.

[e]Missing 10 data points.

[f]Missing 11 data point.

[g]Missing 8 data points.

[h]Missing 2 data point.

[i]Missing 4 data points.

Balance between day-of-surgery and before-day-of-surgery patients on each potentially confounding variable was assessed by the standardized difference (ie, the difference in means or proportions divided by the pooled SD) both before and after weighting by the standardized difference (Table 1). Any variable with an absolute standardized difference greater than 0.28 (ie, $1.96\sqrt{(n_1+n_2)/(n_1n_2)} = 0.28$, where n_1=72 and n_2=166) after weighting by the inverse of its estimated propensity score was considered imbalanced[10] and adjusted for all primary and secondary analyses (we refer to such variables as "unbalanced covariables").

Primary Outcomes. We compared the study groups on the 2 primary outcomes of understanding/comprehension and incremental anxiety in a joint hypothesis testing framework such that day-of-surgery consenting would only be concluded to be acceptable compared with before-day-of-surgery consenting if it was found to be noninferior (ie, not worse) on both the comprehension and incremental anxiety scales. We chose a noninferiority δ of 1 for the anxiety score a priori because on a scale of 6 to 24 a difference of 1 point was not deemed clinically important. We also chose a noninferiority δ of 1 for the comprehension score (range, 0-6) because missing an additional 6 would represent important lack of comprehension.

Because noninferiority on both outcomes had to be significant to reject the overall null hypothesis, no adjustment for testing multiple outcomes was needed for the primary aim. In other words, this was an intersection union test.[11,12]

Thus, with an overall significance level of .05, each test was considered significant if $P<.05$. If noninferiority was found on both primary outcomes, we then planned to assess superiority of day-of-surgery consenting to before-day-of-surgery consenting using 1-tailed tests at the overall .05 level, with Bonferroni correction for conducting 2 superiority tests (significant if $P<.05/2$), because finding superiority on either outcome would be important.

We assessed the noninferiority of day-of-surgery compared with before-day-of-surgery consenting on mean comprehension score with a 1-tailed t test at the .05 significance level and noninferiority δ of 1 point (ie, 1 question). We adjusted for baseline variables by weighting each observation inversely by the propensity score. The null hypothesis (H_0) and alternative hypothesis (H_A) were thus as follows:

$$H_0 : CS_{DOS} - CS_{BDS} \leq -1.0$$

$$H_A : CS_{DOS} - CS_{BDS} > -1.0$$

where CS is the mean comprehension score, DOS is the day-of-surgery group, and BDS is the before-day-of-surgery group. Noninferiority was thus claimed if the difference in means (day of surgery minus before day of surgery) was found to be significantly greater than −1 (ie, day of surgery less than 1 point worse) and correspondingly if the lower limit of the 90% CI (0.05 on lower end) for the difference was greater than −1. Similarly, we assessed the noninferiority of day-of-surgery compared with before-day-of-surgery consenting on mean anxiety score with a 1-tailed t test and noninferiority δ of 1 point on the STAI-SF scale. We used analysis of covariance to compare the 2 groups on postapproach mean anxiety as measured by the STAI-SF scores, while adjusting for anxiety levels immediately before consent (measured with the same tool), weighting each observation inversely by the propensity score, and including unbalanced covariables. We then used the estimated group difference to assess whether day-of-surgery consenting is noninferior to before-day-of-surgery consenting using a 1-tailed t test with a noninferiority δ of 1.

Secondary Outcome 1 (Consent). We assessed noninferiority of day-of-surgery compared with before-day-of-surgery consenting on the proportion enrolled (ie, consented) using a multivariable logistic regression model in which we adjusted for confounding by inverse propensity score weighting and inclusion of unbalanced covariables. Our noninferiority δ was an odds ratio (OR) of 0.70 (30% less likely to consent), chosen a priori to correspond to an absolute difference of approximately 0.50 vs 0.60 in consenting proportion for the day of surgery and before day of surgery, respectively. Noninferiority was thus claimed if the lower limit of the 90% CI for the OR was above 0.70 (−0.357 on log scale).

Secondary Outcome 2 (Perceived Obligation). We compared the day-of-surgery and before-day-of-surgery groups on mean perceived obligation (measured on a 6-point Likert scale) using a linear regression model at the .05 significance level, again adjusting for confounding by inverse propensity score weighting and including unbalanced covariables.

Sample Size. Sample size calculations assumed an estimated ratio of 1:2.5 of day-of-surgery to before-day-of-surgery patients. We based the sample size on being able to detect noninferiority of day-of-surgery to before-day-of-surgery patients on both comprehension and mean anxiety, with an overall 80% power at the .05 significance level. Because both outcomes needed to be significant, we planned for 90% power for each outcome (assuming independence among outcomes, this gives 81% power overall, ie, $0.90 \times 0.90 = 0.81$).

To detect noninferiority for mean anxiety using a 1-point δ with 90% power at the .05 significance level assuming an SD of 2.5 (on the basis of literature), we needed a total of 264 patients. For mean comprehension we needed a total of 102 patients, assuming an SD of 1.7 (on the basis of literature) and using a noninferiority δ of 1. Our actual sample size of 238 was close to the maximum proposed sample size of 264 for these 2 outcomes. Enrollment was stopped at 238 patients for logistical reasons and without access to or consideration of the study results.

RESULTS

Of 238 patients who were approached from February 2011 to November 2011, 72 (30%) were approached on the day of surgery. Patients in the day-of-surgery group were more

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likely to be female, older, and more educated; have a higher RSI; require reading of the materials; be contacted by interviewer A; have less surgical time; and fewer number of questions asked per patient during interview than those who consented before day of surgery (absolute standardized differences >0.28 before adjustment). After adjustment using inverse weighting by the propensity score, balance was achieved for all variables except for RSI (standardized difference, 0.37) (Table 1). Therefore, we adjusted for RSI in all analyses comparing the randomized groups on outcome.

Primary Outcomes

Univariable Summaries. Mean ± SD comprehension scores were 3.8±1.4 for day-of-surgery patients and 4.0±1.4 for those approached before day of surgery. Mean ± SD anxiety scores before and after approaching for consent were 12.4±3.3 and 11.5±3.5 in day-of-surgery patients and 10.7±3.8 and 10.8±3.9 in before-day-of-surgery patients; mean ± SD change in anxiety scores from baseline was −0.82±2.6 in the day-of-surgery patients and 0.12±1.9 in those approached for consent before day of surgery (Table 2).

Main Results. Results of our joint null hypothesis testing are given in Table 3. Because day-of-surgery consenting was found noninferior to before-day-of-surgery consenting on both mean comprehension and mean anxiety, we reject our joint null hypothesis and conclude that day-of-surgery consenting is not worse at the .05 significance level. Specifically, using a noninferiority δ of 1 for each outcome, day-of-surgery patients were found noninferior (ie, not worse) to those approached before day of surgery on both comprehension (mean difference, −0.19; 90% CI, −0.47 to 0.10; $P<.001$) and postapproach anxiety adjusting for baseline anxiety (mean difference, 0.19; 90% CI, −0.29 to 0.68; $P=.003$) at the .05 significance level.

A secondary analysis, assessing anxiety using change from baseline instead of analysis of covariance, also found noninferiority for day-of-surgery consenting ($P<.001$). As expected, the CIs give the same conclusions as the significant P values; the lower limit for the difference in comprehension is above −1 (higher comprehension is better), and the upper limit for postapproach anxiety is less than 1 (lower anxiety is better).

TABLE 2. Univariable Summary of Primary and Secondary Outcomes by Approached Time[a]

Outcome	Approached on day of surgery (n=72)	Approached before day of surgery (n=166)
Primary outcomes		
Comprehension score	3.8±1.4	4.0±1.4
Anxiety score		
After approached for consenting	11.5±3.5	10.8±3.9[b]
Baseline	12.4±3.3	10.7±3.8
Change in anxiety score from baseline	−0.82±2.6	0.12±1.9[b]
Secondary outcomes		
Consented	22 (31)	98 (59)
Perceived obligation	0.3±0.8[c]	0.6±1.1[c]

[a]Data are presented as mean ± SD or No. (percentage).
[b]Missing 2 data points.
[c]Missing 1 data point.

As planned a priori, because noninferiority was found on both primary outcomes, we further tested for superiority of day-of-surgery to before-day-of-surgery consenting for each outcome. Day-of-surgery consenting was not found superior to before-day-of-surgery consenting on either the comprehension score ($P=.14$) or postapproach anxiety score ($P=.26$). Superiority tests were 1-tailed in the same direction as the noninferiority testing.

Secondary Outcomes

Mean perceived obligation did not differ between day-of-surgery and before-day-of-surgery patients in a 2-tailed test for superiority ($P=.55$), with an adjusted mean difference of 0.09 (95% CI, −0.21 to 0.40).

Consent to participate in the POISE-2 research study was 31% in the day-of-surgery patients and 59% in the before-day-of-surgery patients. Day-of-surgery consenting was thus not found to be noninferior compared with before-day-of-surgery consenting on the proportion who consented (adjusted OR, 0.49; 90% CI, 0.33 to 0.72; $P=.46$ for noninferiority). In fact, day-of-surgery consenting was inferior to before-day-of-surgery consenting on proportion who consented ($P<.001$), with the CI for the OR well below 1.0.

DISCUSSION

We evaluated the ethical implications of asking patients to participate in moderate- to high-risk research on the day of surgery. Our

TABLE 3. Multivariable Results of Primary and Secondary Outcomes[a,b]

Outcome	Adjusted mean (SE)[c]		Adjusted difference in DOS-BDS means (90% CI)[d]	δ	*P* value[e]	
	DOS (n=72)	BDS (n=72)			NI	Superiority
Primary outcomes						
Comprehension score (n=238)[f]	3.7 (0.13)	3.9 (0.11)	−0.19 (−0.47 to 0.10)	>−1	<.001	.14
Postapproach anxiety score (n=236)[g]	11.5 (0.22)	11.3 (0.19)	0.19 (−0.29 to 0.68)	<1	.003	.26
Change in anxiety score from baseline (n=236)[f]	0.24 (0.23)	0.21 (0.19)	0.03 (−0.46 to 0.53)	<1	<.001	.46
Secondary outcomes						
Perceived obligation (n=236)[f]	0.68 (0.12)	0.59 (0.10)	0.09 (−0.21 to 0.40)[h]	0	NA	.55[h]
Consented (yes/no) (n=238)[i]	22 (31)[j]	98 (59)[j]	0.49 (0.33 to 0.72)	>0.70	.46	NA

[a]BDS = before day of surgery; DOS = day of surgery; NA = not applicable; NI = noninferiority.
[b]All models are adjusted for risk stratification index and the inverse propensity score, unless noted.
[c]All data are adjusted mean (SE) except for the second outcome of consented (yes/no), which is No. (percentage).
[d]All data are adjusted difference in DOS-BDS means (90% CI) except for the second outcome of consented (yes/no), which is odds ratio (90% CI).
[e]Noninferiority: 1-tailed *t* test with α=.05; superiority: 1-tailed test with α=.025 in direction of DOS.
[f]Multiple linear regression.
[g]Multiple linear regression adjusted for risk stratification index, the inverse propensity score, and initial anxiety score.
[h]The 95% CI and *P* value are from a 2-tailed *t* test for superiority with an overall α=.05.
[i]Logistic regression.
[j]Univariable (unadjusted) proportions; test is adjusted.

primary goal was to evaluate comprehension and incremental anxiety (that is, how much our speaking to the patients increased their anxiety) because these parameters are considered key to ethical informed consent. Other trials have investigated patient comprehension of research protocols.[13-15] However, this is the first study, to our knowledge, to specifically compare consenting on the day of surgery with consenting before that time on patient comprehension. Furthermore, although other studies have examined the association between patient anxiety and comprehension of research protocols,[16,17] this study is the first, to our knowledge, to assess the effect of consent timing on anxiety.

Patients approached on the day of surgery had noninferior understanding (comprehension score, 3.8±1.4 vs 4.0±1.4; adjusted difference, −0.19; 90% CI, −0.47 to 0.10). Patients were understandably more anxious on the day of surgery (12.4±3.3 vs 10.7±3.8); however, the incremental increase in anxiety that resulted from presentation of the POISE-2 protocol was not worse on the day of surgery (−0.8±2.6 vs 0.1±1.9; adjusted difference, 0.03; 90% CI, −0.46 to 0.53). Our major finding is thus that approaching patients on the day of surgery neither reduces understanding of study-related procedures or risks nor increases patient anxiety.

Secondary goals of our study were to evaluate perceived obligation and consent rates. Perceived obligation to participate was no greater on the day of surgery (0.3±0.8 vs 0.6±1.1), although consent rates were significantly lower (31% vs 59%; OR, 0.49; 90% CI, 0.33 to 0.72). Previous work suggests that patients who perceive an obligation to participate in research are less likely to consent.[16] Similarly, other literature indicates that anxiety reduces consent rates.[17] Higher baseline anxiety may thus explain the observed low consent rate on the day of surgery. An additional factor, though, is that many patients wanted to talk with their surgeons before agreeing to the study and there simply was inadequate time or opportunity the morning of surgery.

From a practical perspective, it thus appears preferable to obtain consent from patients before the day of surgery because consent rates are likely to be greater. That said, there is no ethical constraint against approaching patients on the day of surgery for moderate- to high-risk research because day-of-surgery consenting does not reduce comprehension, increase anxiety, or increase the sense of obligation. Patients who, for practical reasons, cannot be approached well before surgery can thus ethically be approached on the day of surgery.

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Our study was conducted in the context of the POISE-2 trial, a moderate- to high-risk protocol. That the trial we presented involved at least moderate risk was important because low-risk protocols would be less likely to provoke anxiety and might thus provide a negative result (no increase in anxiety) that would generalize poorly. POISE-2 is also a factorial design, a concept that some patients may find difficult to grasp.[18] That 2 different medications with different effects and adverse effects were involved further increased complexity. Absolute comprehension (approximately 4 of 6 correct answers) was marginal in both study groups but similar to previous reports.[13-15,19] In fact, studies on patient comprehension of randomization report that this concept by itself is difficult for patients to grasp.[18] Importantly, though, comprehension was no worse on the day of surgery.

The major limitation of our study is that consenting before or on the day of surgery was not randomized because of logistical constraints. A potential consequence is confounding bias because the groups may not have been comparable with respect to important baseline characteristics. For example, patients approached on the day of surgery tended to be less sick (as measured by the RSI) and thus scheduled for less extensive procedures and more likely to be older, female, and highly educated. However, we adjusted for these important potentially confounding variables using propensity score analysis supplemented by multivariable adjustment, thus effectively comparing patients who were well balanced on a wide range of preoperative risk factors and demographic variables on our end points of interest. It thus seems unlikely that bias or confounding explains our results.

The consent process is an individualized endeavor and needs to be suitably adjusted for the concerns, educational level, and cultural expectations of each patient. Prior research reveals that the verbal presentation to the patient is the primary source of information and decision making.[19] In fact, a large part of the consent process itself seems to be on the basis of the patient's perception of having built a trustworthy relationship with the consenter.[20] Despite a carefully developed consent script and a great deal of practice and observation of the 2 consenters involved in the study, no 2 consenters are identical, and no 2 patient encounters are identical. Patients may respond in different ways to different people for no easily discernible reason. Although consenting scripts in this study were highly standardized and every effort was made to ensure each of the 2 consenters had equal exposure to patients in either venue, because of logistical considerations the rates of approach for each consenter were not equal regarding the day of consenting. Our analysis is adjusted for consenter, but given the subtlety of the consent process, it may be difficult to fully account for this effect.

CONCLUSION

In summary, patients approached before or on the day of surgery comparably understood the proposed research, and anxiety was not worsened on the day of surgery. Furthermore, perceived obligation to participate was no worse on the day of surgery, and potential participants were willing to decline the proposed study. In fact, the consent rate was roughly halved on the day of surgery. From a practical perspective, consenting before the day of surgery thus appears preferable, but proposing moderate- to high-risk research on the day of surgery does not compromise essential elements of the consent process.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **IRB** = institutional review board; **OR** = odds ratio; **POISE-2** = Perioperative Ischemic Evaluation 2; **RSI** = risk stratification index; **STAI-SF** = State Trait Anxiety Inventory

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