

ORIGINAL PAPERS

Integrating Patient Preferences in Clinical Trials: A Pilot Study of Acupuncture Versus Midazolam for Gastroscopy

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ABSTRACT

Background and objectives: Patient preferences play an important role when choosing between different treatment options and may have an influence on outcome. We performed a study to investigate (1) to what extent patients make use of the offer to receive acupuncture as a pretreatment for gastroscopy, (2) whether this is perceived as being as effective as sedation, and (3) whether characteristics and outcomes differ between patients giving consent to random allocation and patients choosing their pretreatment.

Design: Partially randomized patient preference trial. Patients who gave consent to randomization were allocated randomly while patients who had a preference received the treatment of their choice.

Patients: One hundred and six (106) inpatients of a district hospital in southern Germany undergoing gastroscopy for diagnostic purposes.

Interventions: Pretreatment with a sedative (midazolam) or acupuncture.

Main outcome measure: Patient's overall assessment on a visual analogue scale (VAS).

Results: Twenty-eight (28) patients (26%) agreed to be randomized, 21 (20%) chose acupuncture, 51 (47%) midazolam, and 8 (7%) did not want pretreatment. Patients receiving midazolam rated the examination as slightly less troublesome than those receiving acupuncture. Oxygen saturation, blood pressure, and heart rate were significantly lower in patients receiving midazolam. Characteristics and outcomes of randomized and nonrandomized patients did not differ significantly.

Conclusions: Because of the low number of patients giving consent to random allocation conclusions on effectiveness are difficult to draw. The partially randomized patient preference design is recommended for use in future trials of acupuncture for gastroscopy. Such trials should be performed in an outpatient setting.

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INTRODUCTION

Patients participating in randomized clinical trials may differ to a considerable extent from patients refusing consent to randomization (Britton et al., 1998; Taylor et al., 1994). As a consequence, the results of a randomized controlled trial might not be generalizable to the population to which the alternative interventions are routinely offered. Clinical trials with designs that take into account patient preferences without sacrificing methodological rigor are therefore desirable and several such designs have been proposed (Brewin and Bradley, 1989; Rucker, 1989; Zelen, 1979). A part of these proposals implies that randomization is performed before informed consent. While this approach has the theoretical advantage of generating comparable groups, it also poses ethical problems. A more realistic option is a design—sometimes called partially randomized patient preference or comprehensive cohort study design—in which patients with distinct preferences receive their preferred treatment while those without preferences are randomized (Brewin and Bradley, 1989). This design has the drawback that it remains unclear whether potential differences in the outcomes of randomized and nonrandomized patients are because of the influence of preferences or because of other differences in patient characteristics. However, partially randomized patient preference studies could simultaneously provide the information (1) of “normal” randomized controlled trials; (2) on actual patient preferences; and (3) on differences in characteristics and treatment outcome between randomized and nonrandomized patients. However, despite the interest in the partially randomized patient preference design, few studies actually using this design have been performed (see Britton et al., 1998, for a review).

We chose the partially randomized patient preference design to investigate whether acupuncture should be offered as an additional option for pretreatment of gastroscopy in a district hospital in Germany. According to surveys from different countries 60% to 85% of all patients undergoing gastroscopy receive sedatives (Froehlich et al., 1994; Quine et al., 1995; Scott, 1995). The most frequently administered

drug is midazolam. While there is empirical evidence that gastroscopy could be performed without sedation in the majority of patients (Al-Atrakchi, 1989; Solomon et al., 1994), those receiving it perceive the examination as less troublesome (Froehlich et al., 1995). Although serious side-effects and complications of sedatives are rare (Froehlich et al., 1994, 1995) the identification of additional effective low-risk methods seem desirable. Acupuncture has been shown to be superior to sham acupuncture in reducing pain, nausea, agitation, and difficulties during the examination in non-sedated patients undergoing gastroscopy (Cahn et al., 1978). Another study showed similar effects in colonoscopy (Li et al., 1991). Two non-randomized controlled studies from China compared acupuncture to intramuscular atropine and diazepam (Chu et al., 1987) or trospium chloride (Ho et al., 1993). Both concluded that acupuncture was an effective alternative to premedication.

Randomized trials comparing acupuncture to midazolam have not yet been performed. Acupuncture and midazolam differ greatly in their physiologic effects and patients are at least partly aware of these differences. Midazolam is mainly sedative and amnesic; as a consequence patients often do not remember details of the examination. Patients receiving acupuncture experience the gastroscopy in a fully conscious state. Different patients are likely to have different preferences for pretreatment and these preferences might have an influence on how gastroscopy is perceived.

The objectives of our study were to investigate (1) to what extent patients make use of the offer to receive acupuncture as a pretreatment, (2) whether this is perceived as being as effective as sedation, and (3) whether characteristics and outcomes differ between patients giving consent to random allocation and patients choosing their pretreatment.

METHODS

Design

All eligible consecutive patients were first asked whether they agreed to their personal data and treatment outcome being docu-

mented. Patients were informed in detail about the three different pretreatment strategies (sedation, acupuncture, neither of the two) for gastroscopy offered in the study hospital. They were then asked whether they agreed to being randomly assigned to receive sedation or acupuncture. If they did not agree they received the treatment of their preference (Fig. 1). Randomization was performed in blocks of 10 using a computer program (Random, idv, Gauting, Germany) and concealed in opaque sealed envelopes that were opened only after the patients had given informed consent to randomization. The study was approved by the regional ethics committee and all patients gave written informed consent.

Patients

All consecutive inpatients above the age of 18 years who were scheduled for an endoscopic investigation of the upper gastrointestinal tract on a day on which an acupuncturist was planned to be available in the ward (about once a week) were screened for eligibility. The schedule for endoscopy was made without knowledge whether an acupuncturist would be available. Exclusion criteria were: a known hypersensitivity against benzodiazepines or local anesthetics, a blood coagulation disorder (international normalized ratio [INR] < 1.91), alcohol or drug abuse, and significant dementia. Pregnant women or nursing mothers were also

excluded. The setting was a primary care district hospital in Simbach, a town in southern Germany, where approximately 500 gastroscopies per year are performed.

Interventions

Patients were informed and gave their consent on the day before gastroscopy. According to random allocation or preference, patients received either midazolam intravenously (up to a maximum dose of 0.06 mg/kg) or acupuncture. Patients who wanted neither sedation nor acupuncture received local anesthetics only. Acupuncture was performed by one of two physicians (a consultant neurologist and one assistant physician) who were trained and experienced in this form of therapy; one had undergone intensive training in Russia and one the standard training (A-diploma) of the German Medical Acupuncture Society. Sterile one-way needles were inserted at the body points CV6, CV12, CV22, bilaterally St36 (depth, 5 mm) and at the ear points stomach, spasmolysis, and *Tai-jang* (1 mm, unilaterally). Needles were left *in situ* during the whole examination and stimulated by manual rotation counterclockwise as needed. All patients received local anesthesia of the throat with 5 puffs of lidocaine spray. Patients who still had strong retching on provocation received another 3 puffs. Additional treatment could be applied as needed but had to be documented. Gas-

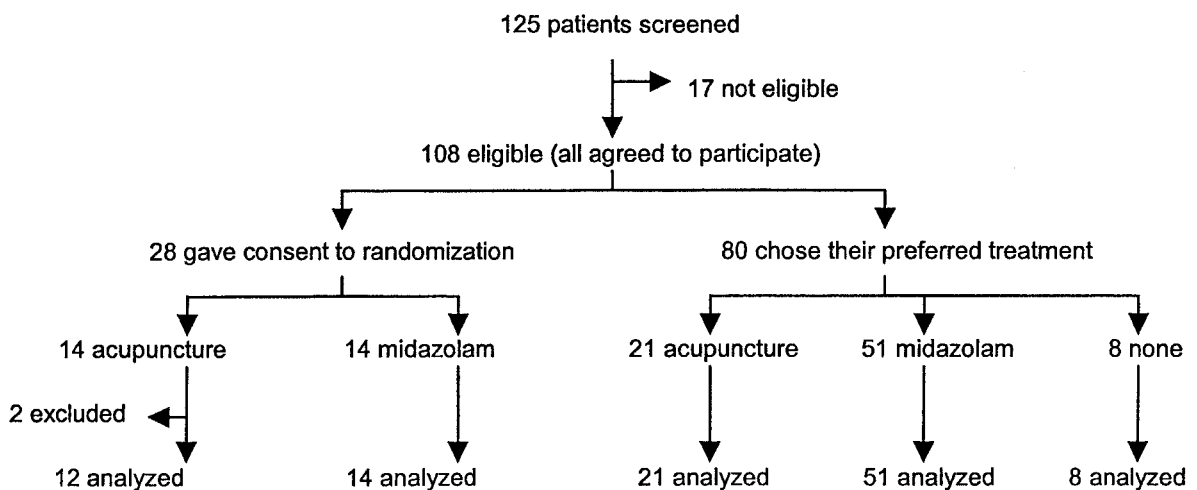


FIG. 1. Trial profile.

troscopy was performed by an experienced consultant using standard endoscopes.

Measurements

After informed consent patients reported their age, gender, weight, consumption of nicotine and alcohol, fear of gastroscopy in general and of different specific aspects. The physician documented the reason for endoscopy and the intensity of retching on provocation. Oxygen saturation (pulse oximetry), blood pressure, and heart rate were monitored automatically (Eagle 1000, Hellige, Freiburg, Germany) and documented before pretreatment as well as before, during, and after gastroscopy. The physician performing the endoscopy or the assisting nurse documented all additional interventions. After completing the examination the physician assessed sedation, difficulties during the examination, retching, and the overall course of the procedure using a verbal rating scale. Side-effects were to be reported on a separate form. Two hours after endoscopy patients were asked to assess the examination. Main outcome measure was the question, "How did you perceive the examination?" (using a 100-mm visual analogue scale with 0 = not troublesome at all, to 100 = extremely troublesome).

Furthermore, patients were asked which pretreatment they would choose for the next gastroscopy, whether they considered the examination less troublesome than expected, and they were asked to rate a number of specific aspects such as retching, pain, etc. For the latter questions they had the possibility to mark a "cannot remember" option.

Statistics

The trial was planned as an exploratory, pragmatic trial. Because of the lack of reliable information on potential effect sizes and differences the parameters for power calculation were set *ad hoc* in the following manner: maximum difference tolerated = 0.5 standard deviations; one-sided test for equivalence, $\beta = 0.2$, $\alpha 0.05$. Based on this calculation we aimed at recruiting 50 patients into each of the two randomized arms. In a pilot case series, approximately 50% of eligible patients stated that

they would give consent to randomization. It was planned to recruit a total of 200 patients in the trial within a period of 18 months. In the analysis, all five groups (randomized to acupuncture, randomized to midazolam, preference acupuncture, preference midazolam, preference no pretreatment) were analyzed separately on a descriptive level in a first step. Then we performed inferential statistics on differences between randomized patients for the main outcome measure (Wilcoxon Mann-Whitney). After checking for differences between randomized patients and those choosing their preference (two-factorial analysis of variance for continuous measures and logistic regression for dichotomous measures), we did an additional comparison between all patients on acupuncture versus all patients on midazolam (regardless of the mode of allocation = pooled analysis). Analysis of variance and logistic regression were performed to check for interactions between allocation status (randomized or not randomized) and treatment status in respect to baseline characteristics and outcomes. All analyses were performed using SPSS (SPSS Inc., Chicago, IL) software.

RESULTS

Because of the low proportion of patients giving informed consent to randomization (26%) and logistical problems (underestimation of the workload associated with obtaining informed consent, acupuncturist less often available than predicted) the trial was stopped after 20 months. Between November 1996 and June 1998, a total of 125 patients had been screened for eligibility; 108 were eligible and all agreed to data documentation. Twenty-eight (28) patients (26%) agreed to randomization: 14 were randomized to acupuncture and 14 to midazolam. Eighty (80) patients (74%) had distinct preferences: 21 (19%) chose acupuncture, 51 (48%) midazolam, and 8 (7%) did not want any pretreatment other than lidocaine. Two patients who had been randomly assigned to acupuncture had to get midazolam because the acupuncturist was not available. These 2 patients were excluded from the analysis. In consequence, the following results are based on the

data from 106 patients (see trial profile in Figure 1).

Demographic features, pretreatment anxiety, and reasons for gastroscopy were similar in the groups, but there were relevant differences between the groups regarding the number of patients with a previous gastroscopy (Table 1). Fear of gastroscopy (after choice or allocation of the pretreatment modality) varied greatly within groups: within each group the degree of anxiety varied between "not anxious at all" and "very anxious." While median values suggest considerable differences between groups these were not statistically significant. Cointerventions and the duration of gastroscopy were similar in the groups. One patient randomly assigned to acupuncture who, because of anxiety, had extremely high blood pressure before acupuncture (246/108 mm Hg), after acupuncture (239/104), and in the first phase of the examination (212/84) received 2.5 mg of midazolam during the further course. There were no significant differences in the characteristics of patients consenting to or refusing random allocation. Patients choosing their preferred treatment were slightly younger than those giving consent to randomization ($p = 0.088$).

Both among randomized and nonrandomized patients gastroscopy was rated as slightly less troublesome by those pretreated with midazolam (mean difference in the pooled analysis 9 mm on a 100-mm visual analogue scale, 95% confidence interval -2 to 20 mm, $p = 0.12$; Fig. 2). Patients who had chosen midazolam

would slightly more often choose midazolam again for their next gastroscopy and found gastroscopy more often better tolerable than expected than those who had chosen acupuncture (Table 2). Up to half of the patients who had received midazolam did not answer the detailed questions on how they had experienced the examination and ticked the "cannot remember" option while almost all acupuncture patients answered these questions.

The physician's assessment of the examination did not differ significantly between groups but moderate or strong agitation occurred less often among patients receiving acupuncture (Table 2). Oxygen saturation was slightly lower in the midazolam group ($p = 0.009$ in the pooled analysis). Acupuncture patients had significantly higher blood pressure and heart rates (Table 2).

Significant interactions between allocation status and treatment status were observed for two (intensity of retching before pretreatment and heart rate during gastroscopy) of 19 variables tested.

DISCUSSION

In this study the majority of patients had clear preferences when given detailed information about the available pretreatment modalities for gastroscopy. Midazolam was the most frequently chosen option but acupuncture was chosen by a relevant minority. Because of

TABLE 1. PATIENT AND INTERVENTION CHARACTERISTICS

	Randomized acupuncture (n = 12)	Midazolam (n = 14)	Preference acupuncture (n = 21)	Midazolam (n = 51)	No pretreatment (n = 8)
Age in years (mean \pm SD)	69 \pm 17	73 \pm 17	62 \pm 16	67 \pm 16	56 \pm 17
Female (%)	42	50	48	65	50
Previous gastroscopy (%)	50	92 ^a	55	68	62
Reason for gastroscopy (%)					
Ulcer/reflux	59	69	52	46	50
Tumor or other	33	23	38	50	25
Both	8	8	10	4	25
Fear of gastroscopy (100 mm VAS, median, range)	35 (0-95)	16 (0-80)	4 (0-100)	25 (0-100)	5 (0-75)
Duration gastroscopy (median, range)	8' (4-16')	9' (5-19')	9' (4-35')	10' (4-30')	8' (4-21')

^aSignificant differences (SD) ($p < 0.05$).
VAS, visual analogue scale.

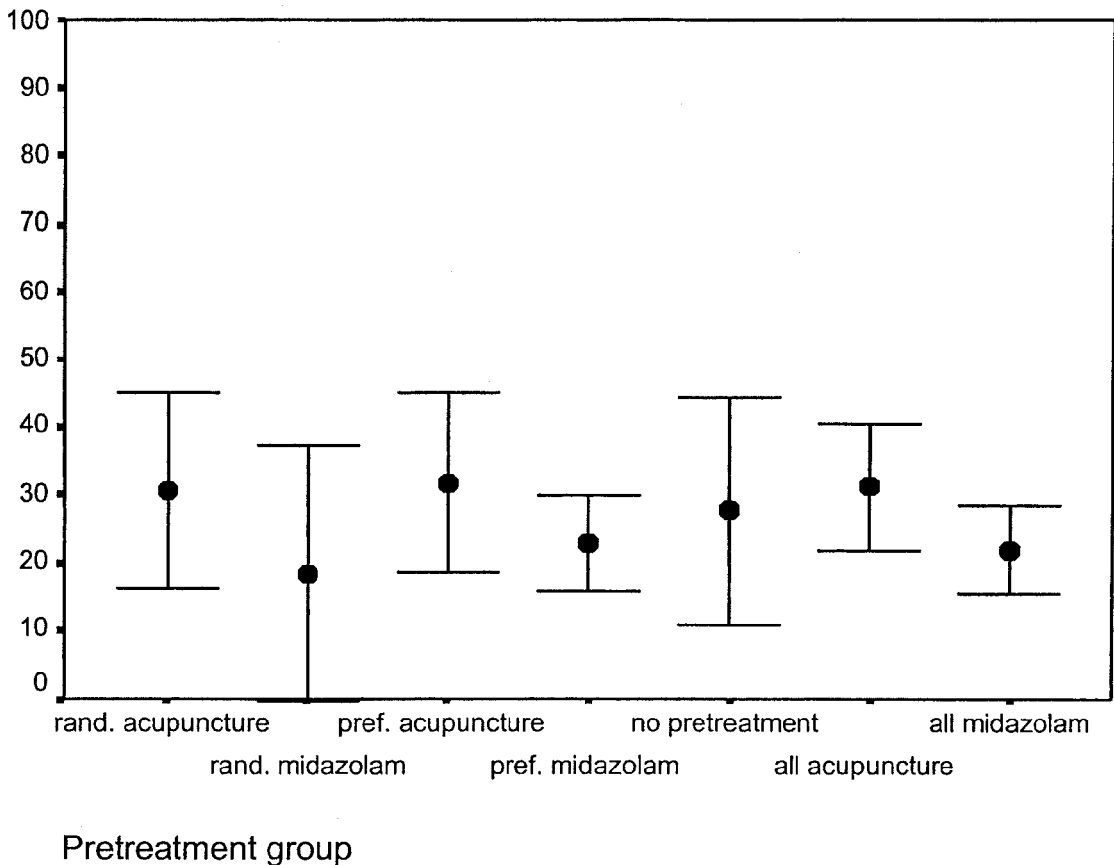


FIG. 2. Mean values (95% confidence intervals) of patients rating on a 100-mm visual analogue scale to what extent gastroscopy was troublesome (0, not troublesome; 100, extremely troublesome).

the lack of statistical power, it is not possible to draw conclusions from the randomized part of the study on whether acupuncture is perceived as similarly effective as midazolam although the results with midazolam seem to be slightly more favorable. We were unable to detect any significant differences between the characteristics and outcomes of randomly assigned patients and those having distinct preferences but this finding also has to be interpreted with great caution due to the limited sample size.

Although the total number of patients included in this study is more than double that of controlled studies of acupuncture in other areas (for example low-back pain trials with a median sample size of 50 [van Tulder et al., 1999], headache trials with 37 [Melchart et al., 1999], osteoarthritis trials with 31 [Ernst, 1997], and asthma trials with 28 patients [Linde et al., 2001]) the fundamental problem of our study

is the failure to meet recruitment targets and the resulting lack of power for the randomized part of the study. Based on a pilot case series we had expected that about 50% of eligible patients would give consent to random allocation but only 26% actually did. With only 26 patients with data suitable for analysis the results of the randomized part of this study is barely interpretable. Whether the analysis pooling randomized and preference patients is interpretable will be discussed below. Under the given circumstances, however, our study can only be considered a pilot study although it was not planned as such.

The acupuncture intervention in our study might not be typical for Western countries. The strategy was chosen by a highly experienced acupuncturist and consultant neurologist who had undergone extensive training in Russia. In the few available controlled trials, acupuncture interventions, as well as the control interven-

TABLE 2. RESULTS IN THE FIVE TREATMENT GROUPS SEPERATELY AND POOLED ANALYSIS OF ALL PATIENTS RECEIVING ACUPUNCTURE OR MIDAZOLAM

	Randomized		Preference		No		All		
	Midazolam	RR/mean diff. ^a	acupuncture	Midazolam	RR/mean diff. ^a	pretreatment	acupuncture	Midazolam	RR/mean diff. ^a
Patient assessment									
Next time the same treatment	8/12	9/14	1.04 (0.59, 1.81)	15/21	46/51	0.79 (0.60, 1.05)	23/33	55/65	0.82 (0.64, 1.06)
Better tolerable than expected	7/12	9/14	0.91 (0.49, 1.68)	10/21	38/51	0.64 (0.40, 1.03)	17/33	47/65	0.71 (0.50, 1.02)
Physician assessment									
Moderate/strong sedation	7/12	10/14	0.82 (0.46, 1.46)	15/21	30/51	1.21 (0.85, 1.73)	22/33	40/65	1.08 (0.80, 1.47)
Moderate/strong agitation	0/12	1/14	0.38 (0.02, 8.65)	1/21	6/51	0.40 (0.05, 3.16)	1/33	7/65	0.28 (0.04, 2.19)
Gastroscopy difficult	3/12	2/14	1.75 (0.35, 8.79)	4/21	15/51	0.65 (0.24, 1.72)	7/33	17/65	1.27 (0.61, 2.64)
Physiological variables (during gastroscopy)									
O ₂ -saturation (%)	95.9 ± 3.0	94.6 ± 3.1	1.3 (-1.1, 3.7)	96.5 ± 2.8	94.2 ± 3.8	2.3 (0.7, 3.9)	96.6 ± 2.4	94.3 ± 3.7	2.0 (1.0, 2.9)
Systolic blood pressure (mmHg)	166 ± 42	134 ± 25	32 (4, 61)	159 ± 31	149 ± 27	10 (-5, 26)	150 ± 27	145 ± 26	17 (3, 31)
Diast. blood pressure (mmHg)	84 ± 12	81 ± 18	3 (-9, 14)	99 ± 15	83 ± 18	16 (8, 24)	101 ± 23	82 ± 18	11 (4, 18)
Heart rate (/min)	99 ± 19	73 ± 13	25 (12, 38)	99 ± 17	83 ± 18	6 (-2, 15)	83 ± 14	81 ± 17	11 (4, 19)

^aRR, rate ratio (rate in acupuncture group/rate in midazolam group) and 95% confidence interval, mean diff. = mean difference and 95% confidence interval.

tions, vary considerably. Cahn et al. (1978) used CV 12, 17, 23, and 24, PC 6, St 36, and Sp 5 (with electrostimulation) in their sham-controlled study; it is unclear whether patients received an anesthetic spray. Chu et al. (1987) compared electrostimulation at St 36 and LI 4 with intramuscular atropine and diazepam; all patients received xylocaine spray. In the trial by Ho et al. (1993) patients in the conventional premedication group received xylocaine spray and intramuscular tropium chloride (an anticholinergic) while patients in the acupuncture groups were treated (without electrostimulation) only at LI 4 and PC 6. All these trials drew positive conclusions.

In 1999 Stellon and Palmer published a trial with some similarities to our study. Two hundred and six (206) patients referred for outpatient gastroscopy were offered intravenous sedation with diazepam. Those who declined sedation were randomly assigned to acupuncture or no intervention (as in our study all patients received xylocaine spray). Ninety-five (95) patients chose sedation, 54 were randomly assigned to acupuncture (at LI 4, PC 6, St 9, CV 23, and 24) and 53 to no intervention (no information was given on the remaining 4 patients). Patients choosing sedation were more often female. Ease of intubation and physical distress were significantly lower in the group receiving sedation while there were no differences between acupuncture and no pretreatment. While patients could choose whether they wanted to be sedated, the design of this trial does not allow investigation of differences between patients with and without preferences receiving the same treatment. Furthermore, it is surprising that all patients who declined sedation gave consent to randomization to acupuncture or no pretreatment.

To the best of our knowledge, our trial was the first in the area of complementary medicine to use the partially randomized patient preference design. This design seems to be a logical tool in areas where strong preferences are expected to exist. However, our trial also reveals the problems associated with this design. One problem is that more patients must be followed considerably increasing the workload of the study. The sample size should, in theory, be sufficient to allow meaningful comparisons of

all comparator groups. Designing and interpreting the statistical analyses is another problem. Methodologists will probably prefer the primary or confirmatory analysis be refined to the randomized subtrial and all additional comparisons be considered sensitivity analyses only.

However, is this necessarily the best in situations like pretreatment for gastroscopy? As mentioned in the introduction there is evidence that gastroscopy can be performed without sedation in the majority of patients. However, there is also evidence that sedation or acupuncture (in the way provided by Cahn et al. [1978]) can decrease discomfort. It seems plausible that different patients will have different preferences. For example, patients anxious about the gastroscopy procedure will probably prefer sedation. Patients who already had endoscopy are likely to be influenced by how they experienced it etc. If preferences matter—i.e., if they influence outcomes—does it make sense to base conclusions only on (the minority of) patients giving consent to randomization? If preferences do not matter, is it then necessary to base the conclusions exclusively on the randomized substudy?

In the few published partially randomized patient preference trials (Henshaw et al., 1993; McKay et al., 1995; Moynihan et al., 1998; Nicolaides et al., 1994; Olschewski et al., 1992; Rovers et al., 2001; Williams et al., 1999) the proportion of patients refusing consent were 42% to 60% (in studies with total sample sizes of 140 to 1694 patients) compared to 74% in our trial. Although in some of the trials there were differences in the characteristics of randomized and nonrandomized patients none found significant differences regarding outcomes. Interactions between treatment and assignment status were observed in some trials for single variables tested but clear patterns did not emerge. In summary, the available partially randomized patient preference trials have not yet shown any clear influences of preferences on outcomes.

So can we rely on the analysis of all patients, no matter whether they were randomized or not? In recent years there have been several systematic reviews comparing the results of nonrandomized and randomized trials (Benson et

al., 2000; Britton et al., 1998; Concato et al., 2000; Ioannidis et al., 2001; Kunz et al., 1998). Collectively the results suggest that randomized and high-quality nonrandomized studies often agree with a tendency for nonrandomized studies to show greater effects in case of disagreements. However, the nonrandomized controlled studies in these analyses aimed to minimize or correct for any differences in patient characteristics and other confounders. We used the partially randomized patient preference design as we expected differences and wanted to take them into account.

As the results in randomized and nonrandomized patients in our study seem consistent we think that the results of the pooled analyses can be interpreted to some degree. Based on the study findings and because of the easier handling of sedation acupuncture will not be offered as a routine option in the hospital where our study has been performed. Because the protracted sedative effects of midazolam and other drugs are more of a problem in outpatients acupuncture is likely to be a more attractive option in such a setting. Future trials should, therefore, preferably be performed in outpatients similar to the study of Stellon and Palmer (1999). Why this study could not reproduce the positive results of the previous trials remains unclear.

Although the available partially randomized patient preference trials provide little evidence for the influence of preferences on outcomes, we think that this design should be used more often, and that it is particularly adequate in subjects like the comparison of different pretreatment options for gastroscopy.

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