Routine versus “on demand” sedation and analgesia for colonoscopy: a prospective randomized controlled trial

Vittorio Terruzzi, MD, Gianmichele Meucci, MD, Franco Radaelli, MD, Natalia Terreni, MD, Giorgio Minoli, MD
Como, Italy

Background: The safety and tolerance of routine sedation and analgesia versus “on demand” sedation were compared in patients undergoing colonoscopy.

Methods: Two hundred forty-nine outpatients were randomly assigned to one of two groups. Group A (n = 125) received midazolam, 0.07 mg/kg intravenously plus meperidine, 0.77 mg/kg intravenously immediately preceding the colonoscope insertion. Group B (n = 124) received the same medication upon request during the procedure. Tolerance was assessed 24 hours later by phone interview performed by a nurse blinded to the medication regimen administered.

Results: Eighty-three patients (66%) in Group B required sedation during colonoscopy. Among men in Group B more than 60 years of age, only 23% required sedation. The proportion of patients reporting moderate or severe pain (34% vs. 12.1%, \( p < 0.001 \)) and of those stating they would not be willing to undergo colonoscopy again in the future (22% vs. 9.7%, \( p < 0.005 \)) was significantly higher in the “on demand” sedation group. By multivariate analysis the randomization group was the single variable independently associated with both such outcomes. The frequency of side effects was similar in the two groups.

Conclusions: Administration of sedative and analgesic drugs routinely before colonoscopy is superior to “on demand” sedation in terms of tolerance and is not associated with an increase in side effects. (Gastrointest Endosc 2001;54:169-74.)

Colonoscopy is generally assumed to be an uncomfortable and even painful procedure. Routine administration of sedative and analgesic drugs is widely provided for colonoscopy in the United States to prevent patient discomfort and increase tolerance for the procedure. The standard practice in some European countries is to begin colonoscopy without premedication and to offer it only when unendurable discomfort or pain is encountered during the procedure. In Italy, there is an extremely high variability in the use of sedation; indeed, the proportion of colonoscopies performed under conscious sedation (either routinely or on demand) ranges from less than 5% to over 90% among different endoscopic units. Nonetheless, the use of conscious sedation during colonoscopy is considered an indicator of quality by most Italian endoscopists.

The main concern regarding the routine use of sedative and analgesic drugs for colonoscopy relates to the fact that sedation accounts for most of the risk of endoscopic procedures, including cardiopulmonary complications and vasovagal reactions, which are considered a leading cause of associated mortality and morbidity. Moreover, sedation and analgesia pose significant economic issues related to costs associated with monitoring, administration of medications, and prolonged recovery time.

In an effort to reduce risk and control costs, sedationless colonoscopy has been introduced. In a recent study it was found that routine sedation with midazolam does not increase patient tolerance to colonoscopy. Therefore, it is still debated whether the benefits of conscious sedation outweigh the risks.

A combination of meperidine and midazolam is commonly used for sedation and analgesia in most Western countries. However, it has been suggested that this combination is not superior in terms of patient tolerance to either drug given alone. In a recent study conducted on a selected population of patients willing to consider colonoscopy without sedation, routine administration of benzodiazepines and meperidine did not result in a significant improvement in patient satisfaction, as compared with as-needed sedation. However, there are no studies among unselected patients comparing routine and “on demand” sedation with benzodiazepines and opioids.

On this basis, a randomized, prospective study was undertaken aimed at evaluating whether sedation and analgesia routinely provided before outpatient colonoscopy are preferable to “on demand” sedation.
PATIENTS AND METHODS

Study design

From August to November 1998, consecutive outpatients undergoing colonoscopy at our endoscopic unit were considered for enrollment in the study. Exclusion criteria were the following: (1) age over 75 and under 18 years; (2) known hypersensitivity to midazolam or meperidine; (3) history of drug addiction; (4) chronic benzodiazepine use, defined as more than 5 doses consumed during the previous week; (5) concomitant serious illness such as severe cardiac or respiratory disease, hepatic encephalopathy, and renal failure (ASA III-IV-V); (6) arterial hypotension, defined as systolic pressure less than 100 mm Hg before colonoscopy; (7) suspected colonic stricture potentially precluding complete colonoscopy; (8) major psychiatric disease (dementia, schizophrenia, and depression); and (9) procedures scheduled on Friday and Saturday, due to the impossibility of collecting patient assessment data the day after the examination. Also excluded were patients who had previously undergone colonoscopy.

Patients who met the inclusion criteria and gave their informed consent were randomly assigned by means of a computer-generated list to two different treatment groups. Group A patients were given midazolam (Ipnovel, F. Hoffmann, La Roche Ltd., Basel, Confederation Helvetica-Switzerland) 0.07 mg/kg and meperidine (Petidina cloridrato, SALF, Bergamo, Italy) 0.7 mg/kg as two separate intravenous boluses immediately preceding the colonoscope insertion. Group B patients were given the same medication only on request during the procedure. All procedures were performed by 6 experienced endoscopists (all having performed at least 300 colonoscopies). However, 3 had more than 10 years of endoscopic experience (range 10-25 years) whereas the others were less experienced (range 2-9 years). For each examination, before obtaining the informed consent from the patient, the endoscopist was blinded to the randomization group. Procedures were performed with videocolonoscopes (EC-3801F, Pentax, Ashai Optical Co., Ltd., Tokyo, Japan) 1820 mm in length. Because it has been reported that patient perception of pain, sedation request during procedure, and renal failure (ASA III-IV-V)13; (6) arterial hypotension, defined as more than 5 doses consumed during the previous week; (5) concomitant serious illness such as severe cardiac or respiratory disease, hepatic encephalopathy, and renal failure (ASA III-IV-V)13; (6) arterial hypotension, defined as systolic pressure less than 100 mm Hg before colonoscopy; (7) suspected colonic stricture potentially precluding complete colonoscopy; (8) major psychiatric disease (dementia, schizophrenia, and depression); and (9) procedures scheduled on Friday and Saturday, due to the impossibility of collecting patient assessment data the day after the examination. Also excluded were patients who had previously undergone colonoscopy.

Monitoring

For all patients, heart rate and oxygen saturation were monitored by means of a pulse oximeter. Spontaneous breathing was visually assessed by a GI assistant throughout colonoscopy, after completion of the procedure, and until the patient was awake. Blood pressure was measured before and after the procedure.

Oxygen desaturation was defined as a saturation of less than 90% for more than 30 seconds. Whenever the oxygen saturation fell below 85%, oxygen at 2 L/min was administered via nasal cannulae and patients were stimulated to breathe deeply.

Endoscopist assessments

After completion of the examination the endoscopist recorded the following data: depth of colonoscope insertion, procedure difficulty (1 = very easy; 2 = fairly easy; 3 = difficult; 4 = failure to complete the examination), procedure duration, endoscopic diagnosis, and level of patient consciousness at the end of the procedure (awake, semi-conscious, or asleep). The duration of the procedure was defined as the time from the insertion of the colonoscope to its removal. If an operative procedure was performed during the examination, this was also recorded.

Patient assessment after examination

The day after colonoscopy, patients underwent a phone interview conducted by a GI assistant who had not been involved in the patient’s care during the examination and who was unaware of the sedation schedule. Patients were asked to report the degree of tolerance for the examination, the degree of pain perceived, and whether they would be willing to undergo another colonoscopy in the future. Tolerance and pain were assessed by means of a semi-quantitative scale (pain: 1 = not at all; 2 = mild; 3 = moderate; 4 = severe; tolerability: 1 = good; 2 = fair; 3 = poor; 4 = unendurable discomfort).

Statistical analysis

For statistical analysis, data were entered into a statistical software program (Intercooled Stata, Stata Corp., College Station, Tex.). For univariate analysis, comparisons between groups were made by means of Student’s t test, chi-square test, or Fisher exact test, as appropriate. Multivariate analysis for qualitative variables (i.e., perception of pain, sedation request during procedure, and willingness to undergo colonoscopy again in the future) was performed by using a logistic step-wise regression model. All parameters having a p value lower than 0.1 at univariate analysis were included and those with a p value higher than 0.3 removed, according to an automat-
Table 1. Clinical and demographic data

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>124</td>
<td>125</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>55.6</td>
<td>54.0</td>
</tr>
<tr>
<td>Gender (male) (%)</td>
<td>53 (42.7%)</td>
<td>57 (45.6%)</td>
</tr>
<tr>
<td>Previous surgery (%) a</td>
<td>23 (18.5%)</td>
<td>16 (12.8%)</td>
</tr>
<tr>
<td>Colonic resection</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Gynecological interventions</td>
<td>19 (15%)</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>38 (30.6%)</td>
<td>27 (21.6%)</td>
</tr>
<tr>
<td>Use of antispasmodic drugs (%)</td>
<td>18 (14.5%)</td>
<td>13 (10.4%)</td>
</tr>
<tr>
<td>Endoscopic diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyps</td>
<td>35 (28.2%)</td>
<td>35 (28%)</td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>21 (16.9%)</td>
<td>19 (15.2%)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>9 (7.3%)</td>
<td>4 (3.2%)</td>
</tr>
<tr>
<td>IBD</td>
<td>3 (2.4%)</td>
<td>8 (6.4%)</td>
</tr>
<tr>
<td>Melanosis coli</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>2 (1.6%)</td>
<td>0 (--)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.8%)</td>
<td>0 (--)</td>
</tr>
</tbody>
</table>


IBD, Inflammatory bowel disease.

aSome patients underwent more than one type of surgery; therefore, the number of procedures differs from the total number of patients.

Baseline data

During the study period, 382 examinations were performed. Two hundred forty-nine consecutive outpatients meeting the inclusion criteria were asked to participate in the study. All gave their informed consent and were thus enrolled. One hundred twenty-four of them were randomly assigned to group A (routine sedation-analgesia before colonoscopy) and 125 to group B (“on demand” sedation-analgesia during the procedure). The two groups were well balanced for all baseline demographic and clinical features considered (Table 1). Indications for colonoscopy included the following: chronic constipation and abdominal pain (n = 114), blood in the stool (n = 68), or one evaluation of abnormalities found on barium enema (n = 37). Miscellaneous indications accounted for the remaining 30 procedures. No significant differences in the distribution of indications were found between the two groups (data not shown).

No significant differences were found between the two groups with regard to fear of the procedure and discomfort due to bowel preparation. Either no fear or a minimal amount was reported by 66 group A patients (53.2%) and 81 in group B (70.4%, p = 0.07). Either no discomfort or a minimal amount during colon preparation was reported by 89 group A (71.8%) and 97 group B (77.6%, p = 0.31) patients.

RESULTS

Table 2. Rate of cecal intubation, duration of colonoscopy and patient assessments of pain, tolerance, and willingness to undergo colonoscopy in the future

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of cecal intubation</td>
<td>116 (93.6%)</td>
<td>120 (96%)</td>
</tr>
<tr>
<td>Duration of examination (mean ± SD, min)</td>
<td>16.9 ± 9</td>
<td>20.1 ± 12</td>
</tr>
<tr>
<td>Moderate or severe pain (%)</td>
<td>15 (12.1%)</td>
<td>43 (34%)</td>
</tr>
<tr>
<td>Good tolerability (%)</td>
<td>106 (85.5%)</td>
<td>89 (71.2%)</td>
</tr>
<tr>
<td>Unwillingness to undergo colonoscopy in the future (%)</td>
<td>12 (9.7%)</td>
<td>28 (22%)</td>
</tr>
</tbody>
</table>


NS, Not significant; SD, standard deviation.

The final endoscopic diagnoses are listed in Table 1. The cecal intubation rate was 116 of 124 in group A and 120 of 125 in group B (93.6% vs. 96%, p = 0.41). In the remaining 13 cases, cecal intubation was not achieved either because of technical problems or the presence of a tight stricture; in no instance was cecal intubation prevented by patient intolerance or poor colon cleansing. The mean procedure duration was shorter in group A (16.9 ± 9 vs. 20.1 ± 12 minutes, p < 0.02) (Table 2). Among patients in group B, the duration of the procedure did not differ between patients requiring and those not requiring sedation-analgesia (18.6 ± 10 vs 20.8 ± 14 minutes, p = 0.36). By multiple regression analysis, 3 variables were independently associated with a longer duration of the procedure: assignment to on-demand sedation, failure to reach the cecum, and polyp removal. The operator judged the procedure fairly easy to very easy to perform in 102 group A and 92 group B patients (82.2% vs. 73.6%, p = 0.12).

Pain and tolerance

The proportion of patients who experienced moderate or severe pain during endoscopy was 12.1% in group A and 34% in group B (p < 0.001); the proportion of patients stating that they would not undergo colonoscopy again the future was 9.7% in group A and 22% in group B (p < 0.005) (Table 2). Multivariate analysis confirmed that assignment to “on demand” sedation was the only variable independent of age and sex, among covariates, to be associated with a high proportion of patients reporting moderate or severe pain and unwillingness to undergo colonoscopy again in the future.
frequently in Group A patients (85.4% vs. 71.2%, p = 0.006) (Table 2). In group B patients, this figure was 8.4% (4/17) among men more than 60 years of age compared with 73% (79/108) among all the remaining patients (p < 0.001). However, among the 13 group B men 60 years and over not requiring sedation, those experiencing moderate or severe pain or were unwilling to repeat colonoscopy were 23% and 38%, respectively. Multivariate analysis confirmed that, among patients assigned to “on demand” sedation, both older age and male gender were independently associated with a lesser probability of requesting sedation during the procedure, whereas no association was found with previous abdominal surgery, regular use of antispasmodic drugs, experience of the operator, completeness of the examination, and need for polyp removal (Table 3).

**Monitoring**

Mean heart rate and blood pressure values before and after the procedure did not differ between the two groups. Oxygen desaturation occurred in 12 patients in group A and 10 in group B (9.7% vs. 8%, p = 0.4). In group B patients, this figure was 8.4% among patients who required sedation and 7% among those who did not (p = 0.55).

**Complications**

A vasovagal reaction characterized by hypotension, bradycardia, and excessive sweating occurred in 4 patients in group A and in 3 patients in group B (all of whom had not required sedation-analgesia). In all, symptoms resolved spontaneously and did not prevent completion of the procedure. No major sedation-related complications occurred in either group. One patient in group A required immediate surgery because of bowel perforation; the postoperative course was uneventful.

**DISCUSSION**

The use of colonoscopy has dramatically increased in recent years, not only as a first-line diagnostic test in symptomatic patients but also as a screening procedure for colon cancer prevention.17-19 However, colonoscopy is generally perceived as an invasive and painful procedure. As a consequence, concerns about patient compliance invariably arise whenever colonoscopy-based screening programs are proposed. For instance, in a sigmoidoscopic screening trial currently in progress in Italy, only 23% of 232,683 subjects contacted by mail responded.20

To increase procedure acceptance, every effort should be made to minimize pain and discomfort. The best strategy to achieve this goal has not yet been defined. In this respect, our data clearly show that routine sedation with midazolam and meperidine is superior to “on demand” sedation. Indeed, the proportion of patients reporting moderate or severe pain and refusing another colonoscopy in the future was 2.5 to 3 times higher for “on demand sedation” than for “routine sedation.” Similar proportions were found in the “on demand sedation” group for patients requesting and not requesting sedation during examination. No association with any other demographic or clinical variable was found at multivariate analysis. Thus, it appears that it is necessary to administer sedative and analgesic drugs before starting the examination because administering “as needed” sedation during the procedure when patients have already perceived some degree of pain does not change the perception of an uncomfortable or painful procedure. Indeed, over 22% of patients randomized to the “on demand” group (i.e., 1 of 5) refused to undergo another examination in the future.

Besides increased tolerance for the procedure, our results show that routine sedation does not augment side effects in terms of episodes of oxygen desaturation and clinically evident vasovagal reactions. Moreover, no differences were found between patients given sedation and those who were not. Hypoxemia is known to occur during unsedated colonoscopy.8,21 However, the frequency of hypotension during the procedure was not evaluated because blood pressure was measured only before and after the examination. The only serious complication (i.e., bowel perforation) occurred in a patient assigned to group A, but this event was not consid-
ered to be sedation-related. To the best of our knowl-
edge, no relation between conscious sedation and
the frequency of perforation has ever been demon-
strated, although it is theoretically conceivable that
the inability of sedated patients to complain of pain
when the colonoscope is being maneuvered could be
a risk factor for this complication.

There are conflicting data on the efficacy of seda-
tion and analgesia in improving tolerance to colo-
noscopy. The contradictory results may be partly
explained by variability in study designs. To our
knowledge, this is the first study comparing routine
versus “on demand” sedation with midazolam and
meperidine in unselected patients.

A common criticism of previous studies evaluating
the use of sedation in GI procedures is selection bias
in patient recruitment. For example, Rex et al.9
reported that among an unselected population invit-
et to take part in a randomized study (routine vs. “as
needed” sedation for colonoscopy), only one third or
fewer of American patients were willing to consider
colonoscopy without sedation.9 A similar proportion
of patients willing to attempt unsedated colonoscopy
was found in another study from the United
States.23 In a preliminary report of another recent
study it was noted that 63% of patients encouraged
to begin colonoscopy without sedation refused.24
Conversely, in our study no patients refused to be
randomized, because in Italy the practice of “on
demand” sedation is much more widely accepted.11

Other aspects of the study design deserve men-
tion. With regard to patient satisfaction assessment,
the levels of procedure tolerance and pain were mea-
sured by means of an arbitrary, semiquantitative
scale. Despite the fact that the scale had not been
previously validated, it has been used in other clini-
cal studies dealing with sedation-analgesia for colo-
noscopy.25,26 There was good concordance between
scores for pain and tolerance and willingness to
repeat the examination, suggesting that the score
system used is reliable. Moreover, this method of
evaluation allowed collection of data by phone inter-
view 24 hours after the procedure. Thus the answers
to the questionnaire were not influenced by the
sedative medication. Finally, the phone interview,
performed by a nurse not involved in patient care
during the examination and blinded to the sedation
schedule, guaranteed, as much as possible, an objec-
tive evaluation of patient satisfaction. It is also note-
worthy that endoscopist experience proved to be
unrelated to the patient outcomes. It is conceivable
that our results are more applicable to the routine
clinical practice than those of other studies in which
all procedures were performed by a single (and usu-
ally highly experienced) operator.

In our study, 66% of patients randomized to the
on-demand group requested sedation and analgesia
during the procedure. By contrast, the proportion
was 23% in a study from Singapore27 and only 5% in
a study from Germany,28 suggesting that wide cul-
tural variability exists in patient attitudes toward
unsedated colonoscopy. In the United States, data
consistently indicate that only a minority of patients
are willing to consider unsedated colonoscopy,9,23
although most of those willing succeed.9

The proportion of patients requesting sedation
was extremely low among men more than 60 years
of age. These same variables were found to be inde-
pendently associated with patient willingness to
undergo unsedated colonoscopy in the study of Rex
et al.9 Male gender proved to be a predictor of will-
ingess to consider sedationless colonoscopy in
another recent study.23 The ability to select a sub-
group of patients who are willing to undergo colo-
noscopy without sedation would reduce risks as well
as costs. However, at variance with the findings of
previous studies,9 our data show a poor degree of
satisfaction, even among older men not requesting
sedation, with 38% of them reporting they would not
agree to undergo another examination in the future.

In conclusion, our study reveals that, in Italy, rou-
tine sedation with midazolam and meperidine is
superior to “on demand” sedation in terms of patient
satisfaction and tolerance.

REFERENCES

1. Williams CB. Comfort and quality in colonoscopy. Gastro-
2. Keeffe EB. Sedation and analgesia for endoscopy. Gastro-
3. Keeffe EB, O’Connor KW. 1989 ASGE survey of endoscopic
sedation and monitoring practices. Gastrointest Endosc
4. Froehlich F, Gonvers JJ, Fried M. Conscious sedation, clini-
cally relevant complications and monitoring of endoscopy:
results of a nationwide survey in Switzerland. Endoscopy
5. Lazzaroni M, Bianchi, Porro G. Preparation, premedication
6. Ristikankare MKO, Julkunen RJK. Premedication for gas-
trointestinal endoscopy is a rare practice in Finland: a nation-
7. Standards of Practice Committee. American Society for
Gastrointestinal Endoscopy. Monitoring patients undergoing
endoscopic procedures. Guidelines for clinical
8. Fennerty MB, Earnest DL, Hudson PB, Sampliner RE.
Physiologic changes during colonoscopy. Gastrointest Endosc
1990;36:22-5.
9. Rex DK, Imperiale TF, Portish V. Patients willing to try colo-
noscopy without sedation: associated clinical factors and
results of a randomized controlled trial. Gastrointest Endosc
10. Froehlich F, Thorens J, Schwizer W, Preisig M, Kohler M,
Hays RD, et al. Sedation and analgesia for colonoscopy: