Anesthesiology 2003; 99:924–8

Acetazolamide Reduces Referred Postoperative Pain after Laparoscopic Surgery with Carbon Dioxide Insufflation

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Background: **Carbon dioxide is the preferred insufflating gas for laparoscopy because of greater safety in the event of intravenous embolism, but it causes abdominal and referred pain. Acidification of the peritoneum by carbonic acid may be the major cause of pain from carbon dioxide insufflation. Carbonic anhydrase is an enzyme that increases the rate of carbonic acid formation from carbon dioxide. Because acetazolamide inhibits carbonic anhydrase, the authors hypothesized that the pain caused by carbon dioxide insufflation may be decreased by the administration of acetazolamide.**

Methods: **A prospective, randomized, double-blind study of 38 patients undergoing laparoscopic surgery during general anesthesia was performed. Acetazolamide (5 mg/kg) or a saline placebo was administered intravenously during surgery. Pain was rated on a visual analog scale (0–10) at four times: when first awake, at discharge from the recovery room, when discharged from the hospital, and on the day after surgery. The site and quality of pain were recorded, as were medications and side effects.**

Results: **Initial referred pain scores were lower after acetazolamide (1.00 ± 1.98; n = 18) than after placebo (3.40 ± 3.48; n = 20; $P = 0.014$), and 78% of patients in the acetazolamide group had no referred pain; however, only 45% patients in the placebo group had no referred pain. Incisional pain scores were not statistically different, and referred pain scores were similar at later times.**

Conclusions: **Acetazolamide reduces referred but not incisional pain after laparoscopic surgical procedures. The duration of pain reduction is limited to the immediate postsurgical period.**

LAPAROSCOPIC surgical procedures are most often performed with abdominal insufflation of carbon dioxide (CO_2), because the risk of sequelae from intravenous gas embolism is greater with less soluble gases like nitrous oxide, air, and helium. Insufflation of CO_2 is painful[1] and usually requires anesthesia or analgesia to be tolerated. Nitrous oxide insufflation has been shown to be less painful than CO_2 insufflation and allows exploratory laparoscopy with regional or local anesthesia.[2,3] Reduction of surgically induced visceral pain has been accomplished by topical lidocaine in awake laparoscopic tubal banding using nitrous oxide insufflation,[4] but results from few studies of awake patients with CO_2 insufflation have been reported.

Bordahl *et al.*[5] studied general compared with local anesthesia and found that pain on CO_2 insufflation was slight in the awake group, although CO_2 was limited to 3 l in volume and alfentanil was administered intravenously immediately before CO_2 was administered. These maneuvers would be expected to reduce pain from CO_2 insufflation. Humidification and heating of insufflating CO_2 also reduce referred pain,[1] suggesting that the dryness of the gas contributes to local tissue desiccation and subsequent injury at the serosal surface. Lennox *et al.*[6] compared spinal and general anesthesia and found that when the steep Trendelenburg position was used during CO_2 insufflation to reduce diaphragmatic exposure to gaseous CO_2 and when intravenous fentanyl was used to treat abdominal or referred pain after CO_2 insufflation spinal anesthesia was an effective alternative to general anesthesia. When performed in the setting of other laparoscopic surgical procedures, postoperative pain studies comparing CO_2 with other insufflating gases showed mixed results, perhaps because of the inability to distinguish between combinations of surgical pain and pain due to CO_2 insufflation.[7,8]

During insufflation of CO_2 in laparoscopic procedures, the production of H^+ at the serosal surface of abdominal organs exposed to gaseous CO_2 is expected to decrease the pH below usual physiologic values and cause pain. Water saturated with 100% CO_2 at atmospheric pressure attains a pH of 3.8 in the absence of physiologic buffers.[9] The actual pH at the serosal surface of the abdominal cavity reflects a dynamic equilibrium between the formation of H^+ from the ionization of dissolved CO_2 and the removal of H^+ and dissolved CO_2 by perfusion of the organ. During laparoscopy with 100% CO_2, an intraabdominal pH as low as 6.24 has been measured in a rat model.[10] Although to our knowledge there are no published studies of pH measurements at the serosal surface during human laparoscopy, pH values in this range have the potential to cause pain unrelated to the surgical procedures.

Carbonic anhydrase is an enzyme that markedly accelerates (catalyzes) the formation of H^+ and HCO_3^- ion formation from CO_2 and water, and 90% of CO_2 is normally carried in human blood as bicarbonate.[11] Catalysts do not change equilibrium concentrations of reactants and products, and hence, neither carbonic anhydrase nor its inhibitors can change the solubility of CO_2, although they may affect the rate at which equilibrium

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Received from the Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin. Submitted for publication February 21, 2003. Accepted for publication May 21, 2003. Support was provided solely from institutional and/or departmental sources.

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concentrations are attained. Acetazolamide is a carbonic anhydrase inhibitor, which decreases the rate of H^+ formation due to enzymatic catalysis. Approved uses for acetazolamide include therapy for glaucoma, prophylaxis for acute mountain sickness, and as an anticonvulsant for a small percentage of patients with refractory seizures. If carbonic anhydrase is inhibited, it may be possible for diffusion or blood flow to remove the acid produced by spontaneous ionization of dissolved CO_2 with sufficient speed to decrease painful stimulation. We hypothesized that the inhibition of carbonic anhydrase reduces postoperative pain associated with CO_2 insufflation by at least 2.0 pain scale units. A sample size analysis suggests that a total of 34 subjects are required to detect a significant difference between two groups with a 0.05 α level and 80% power in a two-sided test of the hypothesis. Adjusting for patients who may not complete the study, we planned to enroll 40 patients in the study.

Materials and Methods

After human research review committee approval and subsequent informed consent by each participant, we investigated the effect of acetazolamide in 41 patients scheduled for laparoscopic surgical procedures. The study was performed in a prospective, randomized, double-blind fashion. Patients were given either 5 mg acetazolamide/kg body weight in saline or 10 ml saline as a placebo after induction of anesthesia. The dose of acetazolamide was chosen based on the acute intravenous treatment of glaucoma, not the chronic oral maintenance dose of acetazolamide. Neither the participants nor the investigators were given the identity of the study medication until after completion of the statistical analysis. The choice of anesthetic was determined by the anesthesiologist assigned to the case without regard for this study.

All patients were older than 18 yr. Patients were excluded from the study for the following: a history of hematologic disease, pregnancy, preexisting metabolic acidosis, respiratory insufficiency or chronic obstructive pulmonary disease, renal insufficiency with a serum creatinine concentration of > 2.0 mg/dl, renal transplantation, preexisting electrolyte abnormalities ($K^+ < 3.5$ mEq/l, $Na^+ < 135$ mEq/l), lithium administration, allergy to sulfonamides, hepatic disease, disorders of the central nervous system, hypovolemia, or diuretic use. Patients with American Society of Anesthesiologists physical status 4 or 5 were also excluded.

Statistical Analysis

The data analyzed included the intraoperative narcotic or analgesic use and analgesic medications given in the PACU. The visual analog scale of pain (0–10) was used in the PACU when the patient was first responsive, on discharge from the PACU, on discharge to home, and the following day. Two pain scores were obtained from each patient at each time, one for referred pain and one for incisional pain. Incisional pain was classified as pain localized to the site of surgery. Referred pain was classified as pain remote from the site of surgery or pain that was diffuse in nature and poorly localized by the patient. When patients had pain that satisfied both criteria, the same numerical value was assigned to both scores unless the patient could clearly assign a different score to each.

The times to discharge from the PACU were recorded as minutes from entry, as were the times to discharge to home for ambulatory surgery patients. The number of emetic episodes, doses of antiemetic medications, and narcotic doses were recorded. Unpaired *t* tests were used to determine the difference of the pain scale at the four discrete times.

Data for patients who reported a range of pain scale values (*i.e.*, 2 to 3) instead of a single number were replaced with the average values. Some of the pain scale measurements were recorded as positive rather than a number because of patient inability to respond with a number. The primary analysis replaced these positive values with a 5 to represent a mid-level pain response, and the sensitivity of this result was examined by replacement with a 3, 5, or 7 to examine any possible differences in results.

For logistic analysis,[12,13] pain scale values less than 5 were treated as "low," and values ≥ 5 were treated as "high." During logistic analysis, when age was considered a categorical variable, age of 35 yr and younger and age of older than 35 yr were used to determine the groups. When weight was considered a categorical variable, weight of ≤ 85 kg and weight of greater than 85 kg were used to determine the groups. For all analyses, the significance level used was $P = 0.05$. The analysis was performed using SAS statistical package version 6 (SAS Institute, Cary, NC). The data are presented as mean $\pm$ SD.

Results

A total of 38 patients completed the study, with 18 in the acetazolamide group and 20 in the placebo group. Of the 41 patients initially enrolled in the study, one patient withdrew consent before the induction of anesthesia. One patient was excluded because the operation was converted from a laparoscopic to an open procedure. One patient (who underwent laparoscopic cholecystectomy) was dropped from the analysis because the study medication was not administered, and the evaluators of the pain scales were not blinded to this fact.

The initial referred pain scores were lower after acetazolamide (1.00 ± 1.98; $n = 18$) than after placebo (3.40 ± 3.48; $n = 20$; $P = 0.014$). The referred pain scores were not different at later times, although a non-

Table 1. Visual Analog Pain Scores (Mean ± SD) for the Acetazolamide and Placebo Groups

Pain Qualifier	Acetazolamide Group (n)	*P* Value	Placebo Group (n)
Initial referred	1.00 ± 1.94 (18)	0.014	3.40 ± 3.48 (20)
Initial incisional	3.64 ± 2.71 (18)	0.799	3.38 ± 3.54 (20)
PACU referred	1.67 ± 3.22 (18)	0.379	2.60 ± 3.24 (20)
PACU incisional	3.28 ± 2.87 (18)	0.762	3.60 ± 3.56 (20)
Discharge referred	2.92 ± 3.58 (12)	0.460	2.00 ± 2.63 (14)
Discharge incisional	3.33 ± 3.28 (12)	0.568	2.57 ± 3.39 (14)
Next day referred	1.71 ± 1.98 (14)	0.753	1.96 ± 2.17 (14)
Next day incisional	2.57 ± 2.28 (14)	0.913	2.68 ± 2.81 (14)

In this analysis, positive scores were replaced by a numerical value of 5. The times of evaluation were the initial symptoms on awakening in the recovery room (initial), on discharge from the PACU, on discharge home for ambulatory patients (discharge), and on the day after surgery (next day).

significant trend toward less pain after acetazolamide was present on discharge from the PACU. Acetazolamide made no significant change in incisional pain scores at any time. The results are shown in table 1. Also of note is that 14 (78%) of 18 patients in the acetazolamide group indicated no referred pain at the initial time, but only 9 (45%) of 20 patients in the placebo group indicated no referred pain. For these data, the Fisher exact test gave a *P* value of 0.041 with an odds ratio for no referred pain with acetazolamide of 4.28 (95% confidence interval, 0.87–23.56).

For the initial pain evaluation, two patients in the acetazolamide group complained of referred pain but could not give a number, and three patients in the placebo group complained of referred pain but could not give a number. Because these patients were unable to adequately use the visual analog scale and give a numerical value between 0 and 10 for their pain, particularly immediately after awakening, a secondary analysis was conducted to determine whether the replacement of a positive indicator of pain with a numerical value of 3 or 7 would alter the statistical significance of the results. As shown in table 2, the statistical significance of the results was not changed by the numerical value used to replace positive indicators of referred pain at the initial time. The results of nonparametric tests remained unchanged.

Because one patient was excluded from the initial statistical analysis due to the failure to give the study drug, the primary and secondary analyses were repeated with the inclusion of this patient in the acetazolamide group, creating analyses based on the intention to treat. In addition, per-protocol analyses were also repeated by including this patient in the placebo group, on the basis of the premise that this patient did not receive the study drug although the pain scale evaluators were no longer blinded. The primary and secondary analyses were not changed in any case using $P < 0.05$ for initial referred pain. Other comparisons remained not significantly different regardless of which group included this patient.

Table 2. Sensitivity of Analysis to the Value Chosen to Represent Presence of Pain (+) for Patients Unable to Give a Numerical Value for Their Pain (Mean ± SD)

Initial Referred Pain Sensitivity Analysis	Acetazolamide Group (n = 18)	*P* Value	Placebo Group (n = 20)
+ replaced by 3	0.78 ± 1.55	0.012	3.10 ± 3.42
+ replaced by 5	1.00 ± 1.94	0.014	3.40 ± 3.48
+ replaced by 7	1.22 ± 2.52	0.022	3.70 ± 3.70

The duration spent in the PACU and the duration before discharge were not significantly different between groups. The age, sex, and weight of the patients were not significantly different between groups. The narcotic use was not significantly different between groups (9.4 ± 6.3 *vs.* 7.1 ± 5.1 mg equivalents of morphine/70 kg body weight for placebo and acetazolamide groups, respectively). Logistic regression models were used to examine possible baseline predictors to high–low pain scale results; none were statistically significant. The odds ratio of having high initial referred pain was 6.55 in the placebo group compared with the acetazolamide group ($P = 0.03$), with a 95% confidence interval of 1.18–36.2. The types of cases in the acetazolamide and placebo groups were similar, as shown in table 3.

Side effects potentially due to acetazolamide were present but were not different between groups. Taste alterations were noted in two patients in the placebo group and also in two patients in the acetazolamide group. One patient in the placebo group complained of poorly fitting contact lenses. One patient in the acetazolamide group complained of feeling strange on the day of surgery in a manner that could not be further characterized.

Table 3. Demographic Data

	Acetazolamide Group (n = 18)		Placebo Group (n = 20)	
Type of Surgery	No.	%	No.	%
Gynecologic	11	61	9	45
Cholecystectomy	3	17	6	30
Gastric bypass	2	11	3	15
Herniorrhaphy	1	5	1	5
Lymph node dissection	1	5	1	5

The patient excluded from analysis because of failure to give the study drug was in the acetazolamide group and underwent a cholecystectomy.

Discussion

Confirmation of Hypothesis

Acetazolamide reduced the initial referred pain scores after laparoscopic surgery with CO_2 insufflation, consistent with our hypothesis. In retrospect, the inclusion of patients in this study with large amounts of surgical pain may have hindered the evaluation of referred pain from CO_2 insufflation, especially when the surgery was in a locale that could potentially cause referred pain in a similar distribution to the referred pain of CO_2 insufflation, such as laparoscopic Nissen fundoplications or laparoscopic gastric bypasses. However, the strength of the study is that in a heterogeneous population, some of whom may have had referred pain as a result of upper abdominal visceral surgery, we were still able to show a decrease in referred pain, suggesting a powerful effect of acetazolamide on referred pain from CO_2 insufflation. This may also be realized by the increased number of patients who noted no referred pain at all. Incisional pain is caused by mechanisms not expected to be altered by acetazolamide, and the lack of reduction of incisional pain by acetazolamide is also consistent with our hypothesis.

Because CO_2 remaining in the abdomen after surgery is expected to be absorbed quickly, the restriction of pain reduction to the initial measurement is also consistent with the proposed mechanism of pain reduction from acetazolamide. Only a single dose of acetazolamide was given in this study, which is generally considered to have an effect for between 4 and 6 h after intravenous administration. The duration of pain relief was limited to this period. The duration of CO_2 pneumoperitoneum after laparoscopic surgery has been radiographically shown to resolve within 6 h in most patients, with only minimal amounts of residual gas in the remainder of patients.[14] Animal studies suggest that subcutaneous emphysema with CO_2 will resolve within a shorter period, perhaps as little as 90 to 120 min.[15] Therefore, extrapolation of findings from the existing literature suggests that treatment of referred pain caused by CO_2 insufflation may only be necessary for this short duration after surgery, but the actual duration of pain relief from acetazolamide can only be determined with further study. In a few cases that lasted over 2 h, the duration of CO_2 pneumoperitoneum might have been better matched to the duration of effect of acetazolamide after surgery if the drug were given near the end of the operation rather than at the beginning. However, most surgeries that we speculate to be appropriate for the use of acetazolamide to reduce referred pain (*i.e.*, those with little surgical pain) are typically short in duration. Redosing acetazolamide could also extend the duration of analgesia in these longer cases.

Optimal Use of Acetazolamide

On the basis of the results and the proposed mechanism, one would expect pain reduction from acetazolamide to be most beneficial in patients undergoing procedures with the least incisional or surgical pain. In these procedures, the referred pain of CO_2 insufflation would constitute most of the postoperative discomfort. Pelvic or low abdominal procedures, in which regional anesthesia is expected to adequately relieve the surgical pain, may be more readily performed without general anesthesia if acetazolamide can reduce the referred pain associated with CO_2 insufflation. If a laparoscopic procedure is performed during general anesthesia, it is possible that the pain reduction from acetazolamide can be accompanied by the administration of smaller doses of intraoperative narcotics, resulting in faster emergence from anesthesia or fewer side effects related to narcotic administration. Diagnostic laparoscopic procedures that are routinely performed with local anesthesia and an insufflating gas other than CO_2 may be possible with CO_2 insufflation, providing its additional safety in the event of intravenous gas embolism with minimal referred pain if acetazolamide is used. Further work must be done to confirm these potential benefits.

Study Limitations and Potential Disadvantages

This was a mechanistic study designed to determine if a difference in referred pain can result from the administration of acetazolamide. It did not compare the efficacy of acetazolamide with standard doses of narcotic or nonnarcotic analgesics. The future role of acetazolamide in laparoscopic surgery cannot be predicted by the results of this study.

It is unclear if any adverse effects may result from the use of acetazolamide in a patient population who also receives CO_2 insufflation. Although no adverse effects were observed in this study, it does not have the power to identify adverse events with a low incidence. The sole reason that CO_2 is used in preference to gases that do not cause referred pain is that its rapid absorption provides safety in the event of this complication. The rapid absorption of intravenous CO_2 is due in large part to its high solubility. Acetazolamide does not change the solubility of CO_2 in blood but merely changes the rate at which CO_2 ionizes. It is not known whether this effect may reduce the safety of CO_2 in the event of an intravenous embolism. It is known that acetazolamide increases the partial pressure difference of CO_2 between arterial and end-tidal gas.[16] Any potential changes in optimal respiratory gas monitoring and patient ventilation due to the increased gradient between arterial and end-tidal values remain to be elucidated.

Acetazolamide, like any diuretic, has the potential to create electrolyte disturbances. Although none were identified in our patient population, this was not rigorously determined in our study and cannot be ruled out.

In addition, acetazolamide may create metabolic acidosis that may worsen any pH change that accompanies hypercarbia associated with narcotic analgesic administration. However, acetazolamide is used as a respiratory stimulant in the treatment of and prophylaxis for acute mountain sickness, because respiratory alkalosis is expected after acetazolamide administration in this setting. The ability to produce analgesia without respiratory depression may represent a beneficial effect of acetazolamide that deserves further study.

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