Alverine citrate plus simethicone reduces cecal intubation time in colonoscopy - A randomized study

Alverin sitrat ve simetikon kolonoskopi'de çekal entübasyon zamanını kısaltır - bir randomize çalışma

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Background/aims: *Successful colonoscopy depends on the insertion of the instrument to the cecum, a detailed examination, and minimal discomfort to the patient during the procedure. The aim of this study was to determine the effects of alverine citrate plus simethicone on the cecal intubation time, colonic spasm and bowel cleanliness.* ***Methods:*** *A prospective, randomized, controlled trial in a consecutive series of patients was conducted to compare alverine citrate as an antispasmodic agent for relaxation of spasm with elective colonoscopy. The drug used consisted of 60 mg alverine citrate plus 300 mg simethicone. Sodium phosphate soda and enema were recommended for bowel cleansing. During colonoscopy, spasticity, difficulty of the procedure, pain, and cleanliness of the colon were scored between 0-4. The time required to reach the cecum was recorded as minutes.* ***Results:*** *Of 165 total patients, 83 and 82 patients were randomized as the drug group (mean age: 51.85±13.47 years) and control group (mean age: 51.68±16.28 years), respectively. There was a statistically significant difference between the groups in the mean time to reach the cecum in favor of the drug group (7.48±3.45 minutes vs. 6.20±3.24 minutes; p=0.02). The time to reach the cecum prolonged with an increase in pain score and difficulty score (p=0.0001 and p=0.001, respectively).* ***Conclusions:*** *Alverine citrate plus simethicone reduced the intubation time significantly by 19%, from 7.48 minutes to 6.20 minutes.*

Key words: Colonoscopy, insertion time, alverine citrate

Amaç: *Başarılı kolonoskopi endoskopun çekuma ulaşmasına, ayrıntılı incelemeye ve işlem sırasında hastanın daha az huzursuz olmasına bağlıdır. Bu çalışmanın amacı çekum entübasyon zamanına, kolonik spazma ve barsak temizliğine alverin sitrat ve simetikon'un etkisini araştırmaktır.* ***Yöntem:*** *Elektif kolonoskopide spazmı çözmek için bir antispazmodik ajan olan alverin sitratın karşılaştırıldığı ardışık hastalardan oluşan bir prospektif, randomize, kontrollü çalışma yapıldı. Kullanılan ilaç 60 mg alverin sitrat ve 300 mg simetikon içeriyordu. Sodyum fosfat soda ve lavman barsak temizliği için kullanıldı. Kolonoskopi sırasında spastisite, işlem zorluğu, ağrı ve kolonun temizliği 0-4 arasında skorlandı. Çekuma erişim zamanı dakika olarak kayıt edildi.* ***Bulgular:*** *Hastaların 83'ü ve 82'si sırasıyla ilaç grubu (ort. yaş 51.85±13.47 yıl) ve kontrol grubu (ort. yaş 51.68±16.28 yıl) olarak ayrıldı. İki grup arasında ilaç grupu lehine ortalama çekum ulaşım zamanı açısından istatistiksel olarak anlamlı bir fark vardı (7.48±3.45 dakikaya karşılık. 6.20±3.24 dakika; p=0.02). Ağrı skoru ve zorluk skoru artışı ile çekuma ulaşma süresi artıyordu (sırasıyla; p=0.0001 ve p=0.001).* ***Sonuç:*** *Alverin sitrat ve simetikon entübasyon zamanını 7.48 dakikadan 6.20 dakikaya %19 oranında anlamlı olarak azalttı.*

Anahtar kelimeler: Kolonoskopi, sokum süresi, alverin sitrat

INTRODUCTION

Colonic spasm is a relatively common problem for endoscopists (1). Although temporary, it may increase the difficulty of colonoscopy, make the procedure painful for the patient and may force the endoscopist to push the instrument further to see mucosa. Antispasmodic agents have been reported as both useful (2-6) and not useful (7, 8) in relieving colonic spasms during colonoscopy. In addition, some endoscopists believe that using an antispasmodic may make endoscopy more difficult by actually decreasing the tone of the colonic muscle (2, 7).

We designed a randomized, single blind, prospective, controlled study to investigate the effects of an antispasmodic drug, alverine citrate plus simethicone (Meteospasmyl ®, Ali Raif İlac Sanayi, Turkey) in colonoscopy. Alverine citrate is supplied as a capsule form used orally, and contains 60

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mg alverine citrate and additionally 300 mg simethicone. Simethicone is an antiflatulent and works by helping the formation of larger gas bubbles. Alverine citrate is a spasmolytic, which has a specific action on the smooth muscle of the alimentary tract (9). It has been used in the treatment of irritable bowel syndrome for many years and indeed is available over the counter for the treatment of irritable bowel syndrome symptoms (9). The usual recommended dosage is one or two 60-mg capsules up to three times daily (9).

MATERIALS AND METHODS

After informed consent was obtained, 165 consecutive volunteer patients (ages 17-78 years) were included in the study, and underwent elective colonoscopy. Patients with glaucoma, obstructive uropathy symptoms, heart failure, renal failure, history of previous colon operation or diagnosis of colon cancer, acute lower gastrointestinal bleeding, allergic reactions to alverine citrate and simethicone, or with a history of bowel obstruction were excluded from the study. Patients were randomized according to the last digit of their medical record number, and were queried by two investigators (EU and YS) about the weekly number of stools and whether they had any abdominopelvic operations, used laxatives, or smoked; for women, the number of pregnancies was also questioned.

Patients drank 90 ml sodium phosphate soda one night before the operation and lavage was performed with 133 ml sodium phosphate 30 minutes before the operation. It was suggested to all patients to eat watery and fiberless food beginning five days before the operation. No sedation or painkillers were used during colonoscopy.

An endoscopist and the endoscopy nurse blinded to the study drug performed the procedure. All colonoscopy procedures were made by two equally experienced gastroenterologists (EA and OS). All colonoscopies were performed by using Pentax EC 3840 L video-colonoscope (Pentax, Japan). Cecal intubation was made by reaching the cecal base as recorded with accurate cecal markers. If indicated, electronic image, biopsy and polypectomy were performed during the colonoscopy. In the drug group (D-group), drug containing alverine citrate was given three times a day for five days, with the last dose given two hours before the operation with minimal water. The control group (C-group) received no drug.

Completion of the colonoscopy was defined as touching the tip of the colonoscope to the cecum. Time of insertion was measured from the time the tip of the instrument entered the anus until it reached the cecum and was referred to as “cecal intubation time (CIT)”. CIT was recorded in minutes and seconds.

After colonoscopy, the level of pain experienced by the patient was measured as follows: 0: no pain; 1: mild; 2: moderate; 3: severe; and 4: very severe (necessitating ending the operation). Other data recorded included CIT, degree of spasm, degree of difficulty, and degree of cleanliness. The degree of spasm was assessed by modified criteria (10). The degree of spasm was scored as follows: 0: no spasm at all; 1: spasm that did not interfere with colonoscope insertion; 2: spasm strong enough to interfere with colonoscope insertion but not sufficient to prevent completion of the colonoscopy; 3: spasm severe enough to prevent completion of the colonoscopy, and/or to push the colonoscope backward out of position, and with intermittent air insufflation needed throughout the examination; and 4: spasm severe enough to prevent completion of the colonoscopy, and/or to push the colonoscope backward out of position, and with continual air insufflation needed throughout the examination. Difficulty was scored as follows: 0: very easy; 1: easy; 2: not easy but not difficult; 3: difficult; and 4: very difficult. Cleanliness was scored as follows: 0: hard stool, more than 50% of the circumference of colon can not be visualized; 1: smooth stool, more than 50% of the circumference of colon can not be visualized; 2: smooth stool, between 25%-50% of the circumference of colon can not be visualized; 3: smooth stool, less than 25% of the circumference of colon can not be visualized; and 4: no stool (11).

Statistical analyses were performed with SPSS version 11 software. Results were indicated as frequency, percent and mean ± standard deviation. Comparisons between the groups were made using chi-square test for gender, smoking, operation, reason for failure, pain, spasm, difficulty, laxative usage, and cleanliness; independent t test for the effect of age, number of stools and number of pregnancies on CIT; Pearson correlation test for the relation between CIT and age, number of stools and number of pregnancies; and one way ANOVA test for the relation between CIT and cleanliness score, pain score, spasm score and difficulty score. These four scores demonstrated variability in a narrow range between 0 and 4. Thus, chi-square test was performed. For the comparison of rank values of

the mean score, Mann-Whitney U test was used. The Kolmogorov-Smirnov test was used in the normal distribution test of CIT, whereas Mann-Whitney U test was used in the abnormal distribution test of CIT. The relationship between CIT and pain score and difficulty score was evaluated by Spearman's rank correlation test. P values of <0.05 were considered statistically significant.

RESULTS

Patient characteristics are shown in Table 1. Of 165 patients, 82 were randomized into D-group (mean age: 51.85±13.47 years) and 83 to C-group (mean age: 51.68±16.28 years). The groups were similar with respect to gender distribution, age, number of pregnancies, smoking, laxative usage, proportion that had undergone abdominopelvic operation, and the degree of spasm, degree of cleanliness, degree of pain, degree of difficulty, and incomplete colonoscopy. It was not possible to reach the cecum in a total of 36 patients (21.8%); 18 (50%) were due to uncleanliness (8 of C-group, 10 of D-group), and the other 18 (50%) refused a further procedure due to pain (9 patients each in D- and C-groups). There was no difference between the groups regarding mean of failure (p=0.61).

According to the results of the normal distribution test of CIT, the p value was found as 0.05. Thus, independent t test was performed, accepting the normal distribution of these data. There was a statistically significant difference between D- and C-groups with respect to CIT in favor of D-group (6.20±3.24 minutes vs. 7.48±3.45 minutes, independent t test; p=0.02) (Figure 1). We observed a 19% decrease in CIT in the D-group, corresponding to a time period of 88 seconds. However, accepting abnormal distribution of these data, the nonparametric Mann-Whitney U test was performed, and a significant difference was found betwe-

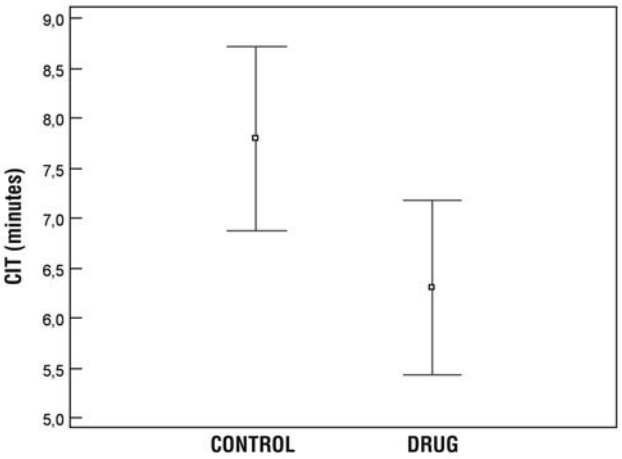

Figure 1. Mean±SD of CIT according to groups. Mean CIT in the control group was longer than in drug group: 7.5 minutes (95% CI: 6.00-9.00) versus 6.2 minutes (95% CI: 5.00-7.00), and this difference (approximately 1.5 minutes) was statistically significant (Mann-Whitney U test, p=0.02).

Table 1. Patient characteristics

Characteristics	Drug Group	Control Group	P value
Patient number	82	83	0.94
Age (mean±SD)	51.85±13.47	51.68±16.28	0.72
Sex (female/male)	40/42	41/42	0.93
Reasons of lack of success (uncleanliness/pain)	10/9	8/9	0.61
Smoking	42	41	0.81
Abdominopelvic operation	23	25	0.77
Laxative usage	14	12	0.66
Colonoscopy indications (n)		Rectal bleeding 44 Constipation 36 Colorectal cancer suspicion 19 Irritable bowel syndrome 19 Abdominal pain 13 Cancer screening 16 Colorectal polyp 6 Other 12	
Colonoscopy diagnosis (n)		Normal 69 Hemorrhoid 40 Diverticula 18 Polyp 14 Colitis 8 Cancer 4 Vascular malformation 5 Other 7	

en D- and C-groups according to the CIT (p=0.01). While it was possible to reach the cecum in women in 7.20±3.54 minutes, the duration was 6.54±3.18 minutes in men (independent t test, p=0.67). There was no effect of age and number of stools on CIT (independent t test, p=0.92 and 0.75, respectively). There was no correlation between CIT and age, weekly number of stools and number of pregnancies (Pearson's correlation test, p=0.59, p=0.82 and p=0.88, respectively). Additionally, there was a relationship between CIT and pain score and difficulty score in D- and C-groups. Both pain score and difficulty score were increased when the CIT increased (r=0.514, p=0.0001 and r=0.656, p=0.001, respectively).

There was no statistically significant difference between the groups in terms of pain, spasm, difficulty and cleanliness scores, and there was also no difference regarding the distribution of these scores (p=0.23, p=0.66, p=0.44 and p=0.59, respectively) (Table 2). Severe colonic spasm (spasm score ≥3) was noted in 84 (50.9%) cases and moderate colonic spasm (spasm score=1 or 2) in 62 (37.6%). Cleanliness, pain, spasm, and difficulty scores showed variability in a narrow range between 0 and 4. Thus, chi-square test was performed by forming a cross table. According to the results, the values of the four scores were seen as similar in both groups. No significant difference was determined between D- and C-groups upon comparison of rank values of the mean score, and according to the results of the Mann-Whitney U test, the values of cleanliness, pain, spasm, and difficulty scores were found as follows: p=0.675, p=0.144, p=0.892, and p=0.400, respectively (Table 3).

Table 2. Distribution of scores between the two groups

Score	Drug group	Control group	P value
Cleanliness			
0	11	8	
1	17	14	
2	14	17	p=0.59
3	24	32	
4	16	12	
Pain			
0	9	8	
1	36	27	
2	18	19	p=0.23
3	9	20	
4	10	9	
Spasm			
0	7	10	
1	24	23	
2	26	21	p=0.66
3	13	19	
4	12	10	
Difficulty			
0	14	12	
1	25	23	
2	22	19	p=0.44
3	8	17	
4	13	12	

P values were estimated with chi-square test to compare scores between the two groups.

Table 3. Mean±SD of scores in each group

Score	Drug group	Control group	P value
Cleanliness	2.21±1.34	2.31±1.19	p=0.675
Pain	1.69±1.18	1.94±1.18	p=0.144
Spasm	1.99±1.18	1.95±1.22	p=0.892
Difficulty	1.77±1.30	1.93±1.28	p=0.400

No significant difference was determined between D- and C-groups when comparing rank values of the mean score, according to the results of Mann-Whitney U test.

CIT was longer at spasm scores 2 and 3 than at spasm scores 0 and 1, and it reached a maximum at spasm score 4 (Figure 2); CIT prolonged with the increase in the difficulty grade. CIT did not vary with the degree of cleanliness.

DISCUSSION

In this study, severe colonic spasm (spasm score ≥3) was noted in 84 (50.9%) cases and mild-moderate colonic spasm (spasm score=1 or 2) in 62 (37.6%). Therefore, in approximately 88% of our examinations, spasm was bad enough to interfere

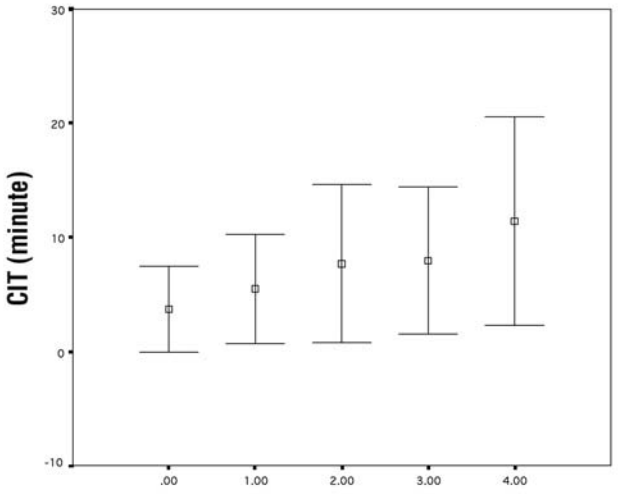

Figure 2. Mean±SD of CIT according to spasm score values. CIT was similar at spasm scores of 0 and 1. While also similar at spasm scores of 2 and 3, CIT was longer than determined at scores 0 and 1, and it reached a maximum at spasm score 4.

with the procedure. The concept that alverine citrate as an antispasmodic drug would relax spasm of the colonic smooth muscle was not confirmed by the data from the present randomized study. Warm water irrigation for dealing with spasm during colonoscopy has been found effective (10) and is also simple and inexpensive.

When antispasmodic agent usage is considered in colonoscopy, it is logical to decrease colonic spasm, which disturbs the visualization of mucosa, causes pain for the patients and prevents the passage of the colonoscope. Thus, a theoretically effective antispasmodic may speed up the insertion of endoscope, may improve the visualization of mucosa and may decrease the pain during the insertion of the colonoscope. However, in the initial studies using antispasmodic premedication in colonoscopy, dicyclomine hydrochloride and glucagon were not shown to be effective (2, 3). Furthermore, the procedure could barely be finished in glucagon-administered patients (3). In 1991, Waxman et al. (4) examined the effects of 0.5 mg intravenous atropine in a prospective, double blind and placebo-controlled trial with 77 patients. They found no statistically significant effect of atropine on the tolerance or easiness of the procedure (4).

In contrast to these initial studies, Saunders and Williams (7) showed the benefit of an intravenous hyoscine-N-butyl bromide. There was a significantly lower intubation time and less colonic spasm in the hyoscine-treated group (a mean of 13 vs. 17.5 minutes; p=0.045), and the procedure could be performed more easily (7). Other studies have since showed the usefulness of hyoscine in colonoscopy (8, 12, 13).

In one study, although there was lower pain score, lower difficulty score and deeper sigmoidoscopy in hyoscyamine-treated patients, the difference was not statistically significant (6). In a randomized, double blind and placebo-controlled trial, it was shown that both oral and intravenous hyoscyamine as a premedication was not effective (5). In our prospective, randomized study where hyoscine n-butyl bromide was used intravenously, it took longer to reach the cecum in the group using antispasmodic (14).

Due to the additional problems, routine conscious sedation is not suggested during colonoscopy (15-19). We also did not use additional sedation. Old age, female gender, low body mass index, constipation and uncleanliness of bowel are suggested as the factors making colonoscopy difficult (20-22). In our study, we found that CIT was not affected by age, gender, cleanliness, number of pregnancies, abdominopelvic operation, laxative usage and pain. These findings are in contrast with the previous reports. However, as the grade of spasm and difficulty increased, CIT also increased. This finding suggests that the prevention of spasm may decrease the time required to reach the cecum. CIT was shortened 1.5 minutes although the drug did not affect spasm score and did not improve other measures. A possible explanation is that the scores that we used were not appropriate. Despite the statistically significant reduction in insertion time, the time saved (~1.5 minutes) may not be clinically important when colonoscopies are performed by expert endoscopists. Whether the drug may be useful in trainee-performed colonoscopy is not known.

Although the usage of alverine citrate and simethicone shortened CIT for a mean of 1.5 minutes, it had no contribution on increasing the cleanliness of colon, relieving colonic spasm or to decreasing pain due to the procedure. It may be considered in patients who will undergo a second colonoscopy due to difficulty in the procedure. Based on our results, using an antispasmodic does not increase the ease of the procedure or patient tolerance; on the other hand, it adds extra cost. The problem of cleanliness of the colon may be overcome by educating the patient, and by using diet and drug. Perhaps the most important issue is to use the best bowel cleansing preparation available; according to Ell et al. (23), the use of preparatory PEG-L1 can be regarded as the “gold standard” for bowel cleansing prior to colonoscopy. An experienced and talented endoscopist does not need an additional premedication, including sedation, by employing various maneuvers that will make the colonoscope pass easily and decrease the patient’s pain.

In conclusion, alverine citrate reduced the intubation time significantly, by 19%, from 7.48 minutes to 6.20 minutes.

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