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Premedication With Single Dose of Acetazolamide for the Control of Referral Shoulder Pain After Laparoscopic Cholecystectomy

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Abstract

Background: The use of laparoscopic surgeries is escalating thanks to their advantages over the open surgeries. However, several complications can be observed following laparoscopy operation. Postoperative pain is a major concern in cholecystectomy surgeries. Pain can be both experienced in operated areas and radiated to the right shoulder. Acetazolamide is used for glaucoma, acute mountain sickness prophylaxis, and epilepsy in few patients with recurrent epilepsy. It seems that patients' pain can be reduced by preventing carbonic acid production in abdomen after operation.

Objectives: We aimed at evaluating if administration of acetazolamide preoperatively could affect early or late postoperative pain following laparoscopic surgery.

Patients and Methods: In a randomized-controlled clinical trial study, 70 subjects (30 - 60 years) scheduled for laparoscopic cholecystectomy were included after obtaining a written informed consent. Patients were divided into two groups randomly (intervention and control). The intervention group received 5 mg/kg oral acetazolamide one hour before the operation. The control group did not receive any further medication.

Results: Administration of a single dose of acetazolamide did not have any statistically significant impact on sleep quality (P = 1.000). Moreover, there was no statistically significant difference between groups regarding nausea and vomiting on single dose administration of acetazolamide (P=1.000). Single dose of acetazolamide was associated with statistically significant decrease in shoulder pain immediately after laparoscopy (P= 0.017). However, there was no statistically significant difference regarding shoulder pain between the studied groups 2, 4, 6, 8, 10, 12, and 24 hours after laparoscopy. Single dose of acetazolamide did not significantly affect analgesic administration in 2, 4, 6, 8, 10, 12, and 24 hours after laparoscopy.

Conclusions: Single dose of acetazolamide was associated with statistically significant decrease in shoulder pain immediately after laparoscopy. However, this effect was limited to the first postoperative hours and it failed to reduce postoperative pain of right shoulder during 24 hours after the operation.

*Keywords:*Premedication, Acetazolamide, Shoulder Pain, Cholecystectomy, Laparoscopic

1. Background

The use of laparoscopic surgeries is escalating thanks to their advantages over the open surgeries. In laparoscopic surgeries, the abdominal cavity is dilated using gases (usually CO_2) for creating essential space needed for instruments use. CO_2 is a non-inflammable gas, which dissolves in blood rapidly and excretes from respiratory system (1).

Postoperative pain has been a major concern for physicians in both traditional and modern medicine (2, 3). Several symptoms/complications can be observed following laparoscopic surgeries (3). Postoperative pain is a major concern in most surgeries (4, 5) including cholecystectomy (6). Numerous methods (4, 5) and medications from analgesics (7) to local anesthetics (8) have been used to overcome postoperative pain. Following laparoscopic surgery, pain can be experienced in surgical area or radiated to the right shoulder. One of the proposed mechanisms is insufflation of CO_2 into the abdomen and its mixture with water and carbonic acid and consequently irritation of surgical and subdiaphragmatic area. Due to common innervation, pain can be sensed also in the right shoulder (9, 10).

Insufflation of CO_2 into the abdomen is almost painful and usually requires general anesthesia. Systemic absorption of CO_2 from peritoneal layers causes hypercarbia ($EtCO_2 > 50$ mmHg), which in turns impacts directly on cardiovascular system and indirectly on the hemodynamics (increase in both the heart rate and arterial blood pressure) through stimulation of sympathoadrenal axis. Production of H+ ion in serous surfaces of abdominal organs during CO_2 insufflation into the abdominal cavity leads to pH decline and pain stimulation consequently. Insufflation of inert gases (e.g. helium, argon) instead of CO_2 has advantages including avoiding an increase in $PaCO_2$ derived from

absorption and its required consequent hyperventilation. Nevertheless, this could be associated with undesirable consequences including but not limited to decreased cardiac output and safety concerns in the event of gas embolism considering the low blood solubility of the inert gases.

Insufflation of nitric oxide instead of CO_2 would be associated with less pain, which would ultimately make laparoscopy possible to be performed with local anesthesia. Reduction of laparoscopy induced visceral pain is feasible and could be achieved without anesthesia and along with nitric oxide insufflation by local anesthesia (6).

Carbonic anhydrase enzyme increases water and CO_2 composition which in turn produces carbonic acid. Acetazolamide inhibits the enzyme, which seems to reduce postoperative abdominal pain through preventing carbonic acid production (11). Previous studies reported acidosis as one of the mechanisms for postoperative pain (12). Furthermore, metabolic acidosis is a known complication of anhydrase carbonic enzyme (13); it declines venous blood pH and the amount of HCO_3 in plasma (13, 14). Considering PH reduction of body fluids, acetazolamide does not prevent abdomen acidosis, even though intensifies acidosis; moreover, it contributes to pneumoperitoneal pain (6).

The onset time of effects for acetazolamide administered orally is about 1 - 1.5 hours and the duration of effect is 8 - 12 hours. Moreover, the time for reaching maximum serum concentration is 2 - 4 hours (15). Almost 90% - 100% of the orally or intravenously administered acetazolamide excretes after 24 hours from kidney (16, 17). Acetazolamide has been approved for glaucoma, acute mountain sickness prophylaxis, and epilepsy in few patients with recurrent epilepsy. It seems that patients' pain can be reduced by preventing carbonic acid production in the abdomen postoperatively (15). Administration of the second dose of acetazolamide prolongs analgesic effects. Diagnostic laparoscopy is routinely performed by local anesthesia and gases other than CO_2; this can be performed by CO_2 insufflation with high safety regarding venous gas embolism and with lowest referral pain. Nevertheless, acetazolamide has no effects on solubility level and rapid CO_2 absorption consequently (18).

2. Objectives

We aimed at evaluating if administration of acetazolamide preoperatively could affect early or late postoperative pain following laparoscopic surgery.

3. Patients and Methods

In a randomized-controlled clinical trial study, 70 subjects (aged 30 - 60 years) scheduled for laparoscopic cholecystectomy were included after obtaining written informed consent. Subjects were divided into two groups randomly (intervention and control). Exclusion criteria were addiction, history of psychopathy, patients' refusal, underlying disease (neuropathies), drug allergy to sulfonamides, renal insufficiency, COPD or respiratory diseases, pregnancy, hematologic disease, acidosis, kidney transplantation, electrolyte disorders, use of lithium or diuretics, CNS disorders, liver diseases, existence of any disorder in the right shoulder, previous muscular diseases, and hypovolemia.

The intervention group (group I) received 5 mg/kg oral acetazolamide one hour before the operation. The control group (group C) did not receive any medication. Premedication was performed by midazolam 0.05 mg/kg and fentanyl 1 μg/kg before anesthesia induction. Induction was performed by propofol 2 mg/kg and atracurium 0.8 mg/kg. Intubation was performed after complete relaxation and semi-sitting position was maintained afterwards. Anesthesia was maintained with isoflurane and N_2O. After the operation, pain severity was assessed on the shoulder and incision area by VAS at 0, 2, 4, 6, 8, 10, 12, and 24 hours. Administration of analgesics was recorded on considered hours. The quality of sleeping, nausea and vomiting were also assessed.

A sample size analysis suggested that a total of 62 subjects are required to detect a significant difference between the two groups with $\alpha = 0.05$ and 80% power in a two-sided test of the hypothesis, but to consider possible lost to follow-up we included 70 subjects.

Data was analyzed using descriptive, T test, Chi square test, and F test methods by SPSS version 9.0 (SPSS, Inc., Chicago IL, US). Repeated measure test was used for evaluating pain severity in various times. P value less than 0.05 was considered statistically significant. Data distribution normality was evaluated using Kolmogorov–Smirnov test and QQ-plot. This study was registered in Iranian Registry of Clinical Trials as IRCT2014071117 72N15.

4. Results

The mean age of subjects was 46.56 years with mean of 43.71 and 43.4 years in I and C groups, respectively. Among patients, 59 subjects were female and 11 males. Pain score mean before the operation was 0.43 and 0.63 in I and C groups, respectively. In group C, 3 patients (8.6%) had bad quality of sleeping, 22 patients (62.9%) with medium quality of sleeping and 10 patients (28.6%) with good quality of sleeping. In contrast, in the intervention group, 2 patients (5.7%) had bad quality of sleeping, 26 patients (74.3%) with medium quality of sleeping and 7 patients (20%) with good quality of sleeping. Administration of single dose of acetazolamide had not any statistically significant effect on sleep quality ($P = 1.000$). Furthermore, there was no statistically significant difference between the groups regarding nausea and vomiting on single dose administration of acetazolamide ($P = 1.000$). Shoulder pain level in the intervention on zero hour and control is demonstrated in Table 1.

Single dose of acetazolamide produced statistically significant reduction of shoulder pain at hour zero (immediately) after laparoscopy ($P = 0.017$). However, there was no statistically significant difference regarding shoulder pain at hours 2, 4, 6, 8, 10, 12, and 24 following laparoscopy. Furthermore, single dose of Acetazolamide was not associated with any statistically significant difference on the analgesic administration at hours 0, 2, 4, 6, 8, 10, 12, and 24 following laparoscopy.

Table 1. Shoulder Pain Level in the Intervention on Zero Hour and Control[a]

Pain Score (Hour 0)	Subjects
Intervention	
5	0 (0)
4	1 (2.9)
3	4 (11.4)
2	9 (25.7)
1	0 (0)
Control	
5	1 (2.9)
4	5 (14.3)
3	7 (20)
2	8 (22.9)
1	2 (5.7)

[a]Data are presented as No. (%).

5. Discussion

This study showed that acetazolamide did not have significant effect on pain level of the right shoulder during 24 hours after the operation. Woehlck et al. (9) and Hanly et al. (10) studies demonstrated that acetazolamide injection can decline referral pain, but not incision pain. Statistically significant difference was not observed regarding referral pain decrease between the intervention and control groups (9, 10).

Tissue acidosis has been introduced as a mechanism of pain creation in Issberner et al. study (19). Reduction of venous blood pH and volume of plasma HCO_3 at the same time due to diuretic effect of HCO_3 from kidney has been demonstrated (12, 13).

Based on Singh et al. study, adding acetazolamide to a multimodal regimen could improve pain management in patients undergoing laparoscopic nephrectomy (14). Radhakrishnan et al. (20) reported that acetazolamide reverses thermal hyperalgesia with an inflammatory origin, but mechanical allodynia did not change. Statistically significant difference was not observed between the two groups (20). In Moazeni-Bistgani et al. (21) study, 250 mg oral acetazolamide was administered 24 hours before laparoscopic cholecystectomy and continued every 8 hours until 24 hours after the operation. Although previous studies showed that acetazolamide reduces peritoneal washing fluid pH and decreases referral right shoulder pain, acetazolamide can induce abdominal pain on incision area and right shoulder pain after 24 hours by making tissue acidosis. Consequently, a statistically significant difference has been reported only on hour zero after laparoscopy following administration of acetazolamide (21). Our study had some limitations; for instance, our study was not blinded.

Overall, acetazolamide could be effective only in the immediate postoperative period and it had no confirmed effects on shoulder referral pain following laparoscopy surgery. However, further studies with larger sample sizes are required to confirm this.

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Footnote

Authors' Contribution: Reza Movassaghi provided the hypothesis and the draft, Ali Peirovifar and Davood Aghamohammadi collected data and revised the final draft, Hassan Mohammadipour Anvari, Samad EJ Golzari and Zohreh Kourehpaz provided the revised manuscript, collected data and performed the analysis.

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