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Systematic Review and Meta-Analysis of Perioperative Administration of Acetazolamidefor Management of Postoperative Pain After Laparoscopy

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Systematic Review and Meta-Analysis of Perioperative Administration of Acetazolamide for Management of Postoperative Pain After Laparoscopy

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Introduction

Laparoscopy (LSC) for abdominal surgery has become the standard approach for many surgical interventions to date. While there are numerous benefits to a minimally invasive technique, LSC can also be associated with postoperative referred pain to the shoulder. Laparoscopic (LSC) surgery has added benefits over laparotomy, including shorter hospital stays and potential decrease in postoperative pain leading to decreased opioid use. However, it does require insufflation of the abdomen for visualization, and this is most often achieved with carbon dioxide (CO2) (Figure 1).

While several interventions have been proposed to mitigate this pain, no singular intervention has proven to be superior. Perioperative acetazolamide (ACTZ) administration is a relatively cost effective and safe option, though it is less well recognized, and its efficacy is currently unproven.

ACTZ is a medication that works by inhibiting the carbonic anhydrase enzyme, which is responsible for the conversion of CO2 and water to carbonic acid. The CO2 gas that is used for insufflation is converted to carbonic acid by carbonic anhydrase, leading to intraperitoneal irritation due to acid buildup.

Perioperative administration of ACTZ may decrease the amount of carbonic acid production and thereby decrease diaphragm irritation. This represents a potential cost-effective strategy with few side effects or contraindications, making it an ideal option for improving postoperative pain.

This study was designed as a systematic review and meta-analysis to evaluate the efficacy of perioperative ACTZ administration with LSC for reducing postoperative referred pain.

Methods

A systematic literature search was performed and included studies published from inception to March 1, 2020. We included only studies of patients who underwent abdominal LSC, had a pain assessment at approximately 24 hours postoperatively, and included a treatment with ACTZ for pain management group and a no-treatment or minimal-treatment comparison group. Five studies met inclusion criteria, with a combined total of 253 participants, 116 in the ACTZ group and 137 in the control group. A Bayesian hierarchical model was assumed for the study specific treatment effects. Posterior sampling was conducted via Markov Chain Monte Carlo methods, and posterior inference carried out on the hierarchical treatment effect.

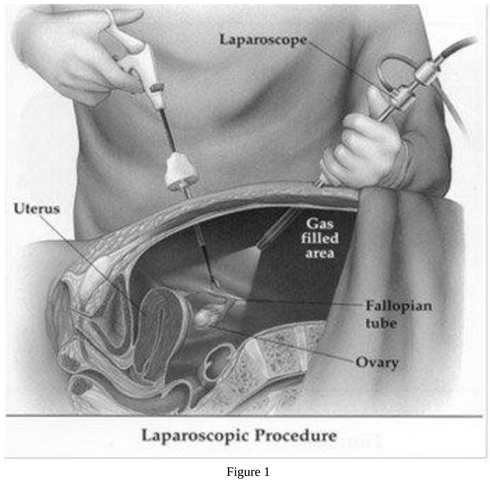


Figure 1

Results – Individual Study Outcomes

A summary of the study characteristics is exhibited in Table 1. Two of the studies involved patients undergoing laparoscopic cholecystectomy [3, 5]. One study included patients underwent LSC for donor nephrectomy [6]. Another study included patients who were undergoing inguinal herniorrhaphy [4]. The final study included patients receiving LSC for several different surgical procedures, including gynecologic, cholecystectomy, gastric bypass, herniorrhaphy, and lymph node dissection [7].

Study	Study design	Intervention (n)	Outcome	Main findings
Singh R et al. 2009[6]	RCT	• Acetazolamide and bupivacaine (40) • Bupivacaine (40)	Postoperative pain intensity using VAS	Acetazolamide + bupivacaine group had reduced postoperative pain scores compared to bupivacaine only group
Pourladian et al. 2016[4]	Observational	• Acetazolamide (22) • No acetazolamide (44)	Postoperative pain intensity using VAS	Acetazolamide group had reduced postoperative pain scores compared to no acetazolamide group
Woehlck HJ et al, 2003[7]	RCT	• Acetazolamide (18) • Saline placebo (20)	Postoperative pain intensity using VAS	Acetazolamide group had reduced postoperative pain scores compared to saline placebo group
Rahimzadeh R et al, 2018[5]	RCT	• Acetazolamide (20) • Bupivacaine (20) • Saline placebo (20)	Postoperative pain intensity using VAS	Acetazolamide group had reduced postoperative pain scores compared to saline placebo group
Bala I et al, 2015[3]	RCT	• Acetazolamide (20) • No Acetazolamide (20) • Saline Placebo (20)	Postoperative pain intensity using VAS	Acetazolamide group and saline group had similarly reduced postoperative pain scores compared to no acetazolamide group

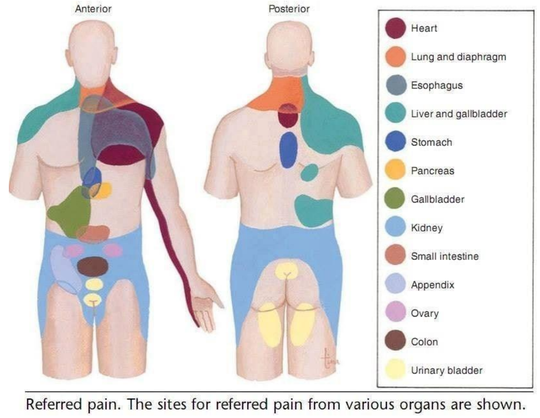
Table 1

Results – Effect of Acetazolamide on 24-hour pain score

The average and standard deviation of VAS scores for the ACTZ and control groups used for posterior sampling are shown in Table 2. The largest observed mean difference in 24-hour VAS scores between the control and ACTZ groups was 1.7, which was seen in Pourladian et al. Of interest, the standard deviation of VAS scores in the ACTZ group was smaller than the control group, despite having half the sample size. The weighted average VAS scores across all the studies was 2.45 for the ACTZ group and 3.35 for the control group, respectively. The posterior mean for the hierarchical treatment effect was -0.726 (95% Credible interval = -1.175, -0.264) indicating that ACTZ decreases average pain scores compared to control. The posterior probability that ACTZ reduced pain scores (i.e. P[τ<0|Data]) was 0.997. This is nearly definitive evidence that ACTZ can be used therapeutically. The posterior probability that ACTZ decreases mean pain scores by 0.5 or more was 0.846.

Study	N Acetazolamide	Mean (SD) 24hr pain score - Acetazolamide	N Control	Mean (SD) 24hr pain score - Control
Singh et al	40	1.15 (1.44)	39	1.67 (1.67)
Pourladian et al	22	2.3 (0.9)	44	4 (2.1)
Woehlck et al	14	1.71 (1.98)	14	1.96 (2.17)
Bala et al	20	6 (0.75)	20	6 (1)
Rahimzadeh et al	20	2.22 (0.63)	20	3.55 (1.12)

Table 2

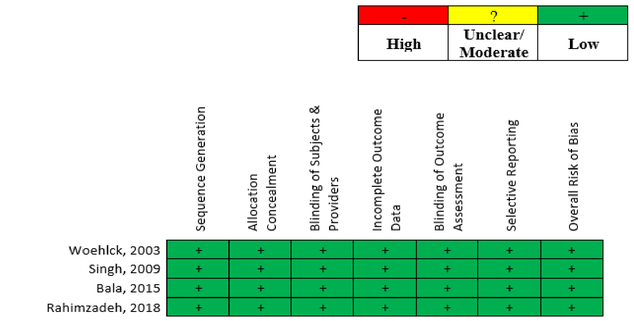


Referred pain. The sites for referred pain from various organs are shown.

Figure 2

Risk of Bias Analysis

A.



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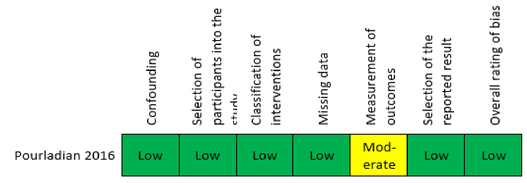

Figure 3

Risk assessment outcomes are shown in Figure 3. (A) Using the Cochrane Risk of Bias in Randomized Trials (RoB 2.0) tool for randomized controlled trials, all seven domains revealed a low risk of bias for the four articles within which randomized controlled trials were executed for data ascertainment. (B) Using the Cochrane Risk Of Bias In Non-randomized Studies (ROBINS-I) tool, all domains were determined low risk of bias, except measurement of outcomes was considered moderate.

Conclusions

- Our study found perioperative acetazolamide administration resulted in moderate, decreased pain the day after a laparoscopic procedure. This intervention is a reasonable adjunct to a minimally invasive procedure to potentially decrease pain, shorten hospital stays, improve patient satisfaction, and decrease the need for postoperative pain control.
- Given the diversity of procedures in this analysis, the external validity of our findings allows consideration for this intervention to be applicable across the minimally invasive spectrum.
- Our study design does not allow for any conclusions to be drawn regarding adverse side effects of acetazolamide, though the studies reporting on adverse events were overall reassuring.
- A well-defined, blinded, prospective randomized trial with a set dose of acetazolamide compared with placebo would be most appropriate to further knowledge in this area.