

# A Randomized Double-Blind Controlled Proof-of-Concept Study of Alanyl-Glutamine for Reduction of Post-Myomectomy Adhesions

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## Abstract (Submitted for Publication)

**Background:** The myriad medical and financial burdens of post-operative adhesions are well documented; however, treatment options are limited and controversial. Implantable physical barriers to prevent adhesions are commercially available, but most trials have failed to demonstrate compelling evidence to support widespread use. In recent years, advances have been made in our understanding of the cellular mechanisms underlying adhesiogenesis, raising the prospect of targeting these pathways to prevent post-surgical adhesions. However, to date, no drug has received regulatory approval for this purpose in any jurisdiction. Our study was designed to evaluate the efficacy and safety of a single intraoperative intraperitoneal dose of L-Alanyl-L-Glutamine (AG), an agent which has been shown to act upon key mediators in the adhesion formation pathway.

**Methods:** This was a randomized, double-blind, placebo-controlled study (DBRCT) of 38 women who underwent myomectomies by laparoscopy (N=38; AG-19 vs Placebo-19) or laparotomy (N=10; AG-5 vs Placebo-5) with a scheduled clinically necessary second-look laparoscopy (SLL) 6 - 8 weeks later. Digital recordings were obtained for all procedures. The primary endpoint was reduction in the incidence, severity and extent of post-operative adhesions, as analyzed by intention-to-treat (ITT) approach. Three independent, blinded reviewers evaluated the operative video recordings to assess for presence of adhesions. Secondary endpoints assessed the safety and tolerability of AG. Posthoc analysis assessed presence or absence of adhesions in the peritoneal cavity.

**Results:** Thirty-two patients in the laparoscopy arm completed SLL. Adhesion prevention was achieved in 15 of 15 (100%) in the AG treatment group versus 5 of 17 (29.6%) in the placebo group. Administration of AG reduced the incidence, severity and/or extent of post-operative adhesions (p=0.0456). The presence of adhesions in the AG group was lower than that in the Control group (P=0.0411). No serious adverse events were reported. No differences in safety parameters were observed between groups.

**Conclusions:** Intraperitoneal L-alanyl-L-glutamine reduced adhesion formation following laparoscopic myomectomy. Results confirm AG's known in vitro effects on cellular mechanisms of adhesiogenesis and lays the groundwork for a potential paradigm shift in adhesion prophylaxis research and treatment.

ClinicalTrials.gov ( [NCT04250467](https://clinicaltrials.gov/ct2/show/study/NCT04250467)).

**Key Words:** Post-operative Adhesions, Myomectomy, Laparoscopy, Randomized Control Study, Glutamine, Evitar™