

PERIDAN™ Gel and Solution Safely Inhibit Postsurgical Adhesions in Two Rat Models

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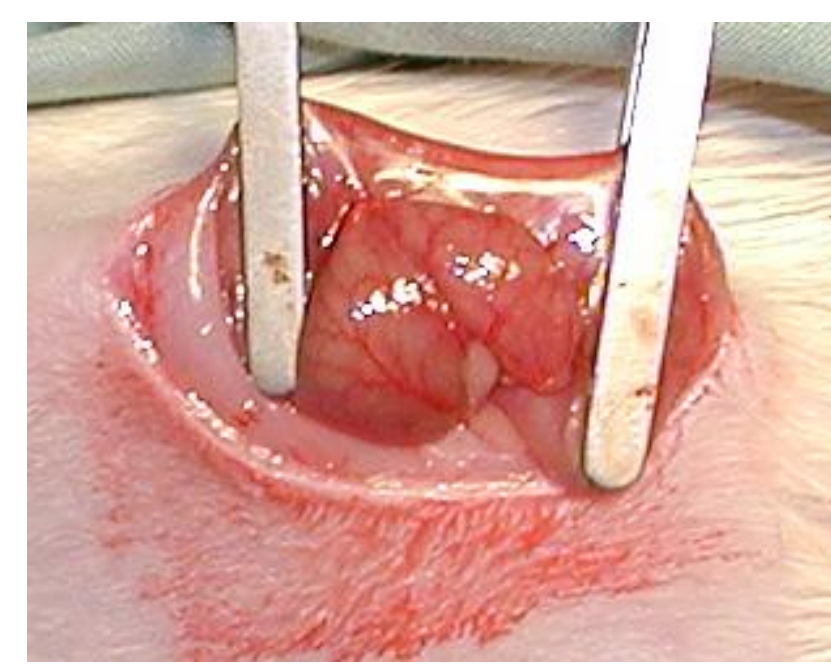
INTRODUCTION

Despite recent advances in surgical techniques and the development of new anti-adhesion agents, complications arising from post-surgical adhesions are still a major cause of female infertility. Adhesions occur when ischemia, foreign material or infection disrupts the peritoneum and initiates an inflammatory cascade that culminates in the formation of dense fibrous bands between affected organs. Over the past few decades the proportion of surgeries that are performed by laparoscopy rather than open procedures has increased. The advantages of a laparoscopic approach to surgery are numerous, and include less postoperative pain, lower incidence of infection, early return of bowel function and ambulation, reduced rates of ventral incisional hernia, less intraoperative blood loss, improved cosmesis, and a lower economic burden. While a number of clinical and experimental studies comparing rates of adhesion formation between laparoscopic and conventional open procedures have demonstrated a decrease in adhesions-related complications after laparoscopy, others have found a comparable incidence of adhesions following either technique. The most commonly used agents for adhesion prophylaxis are barrier methods that are not suitable for laparoscopic application. A gel or liquid solution that could be administered through a laparoscope trocar would be more appropriate for closed procedures. The aim of the present work was to prepare gel and liquid solution formulations containing fucoidan, a high molecular weight polymer extracted from marine algae, and to examine their safety and efficacy in rat caecal-sidewall and uterine-horn surgical models.

METHODS



The abdominal wall was retracted to permit excision of the peritoneum. A single stitch was made at each of the lower corners of the abraded area to the abraded caecum. The gel was placed between the abraded area and the caecum.



The upper margin of the caecum was then attached to the upper border of the abraded area by two corner stitches.

Figure 1. Surgical procedure used in the rat caecal-sidewall model for surgical adhesion. The caecum and sidewall were injured and stitched together. Seven days post-surgery the animals were sacrificed for adhesion assessment. The adhesion strength was scored from 0 (no adhesions) to 3 (dense adhesions with unavoidable tearing of tissue). The extent of adhesion formation was quantified by assigning a value of 1 to 4 according to the total area of the peritoneal defect involved. A final Adhesion Value for the caecum-sidewall area was then calculated by multiplying the two numbers. The maximum Adhesion Value in this model is 12.

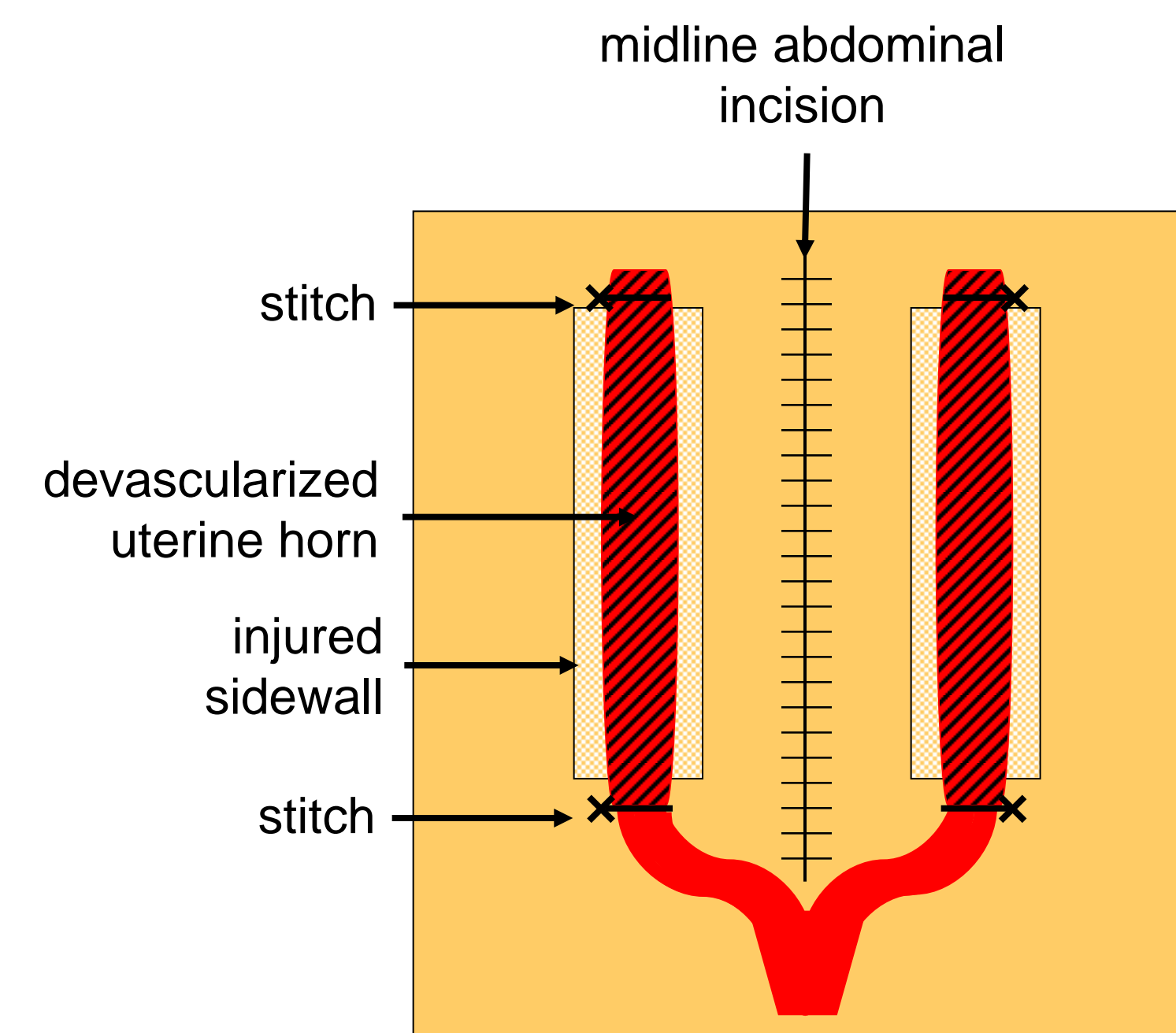


Figure 2. Surgical procedure used in the rat uterine horn model for surgical adhesion. The uterine horn was devascularized and the sidewall injured and sutured loosely together. The animals were sacrificed seven days post-surgery for adhesion assessment. Adhesion strength and extent were evaluated as in the caecal-sidewall model. An adhesion score for each horn was then calculated by multiplying the two numbers. The final Adhesion Value for each rat was obtained by adding adhesion scores from each uterine horn. The maximum Adhesion Value possible in this model is 24.

RESULTS

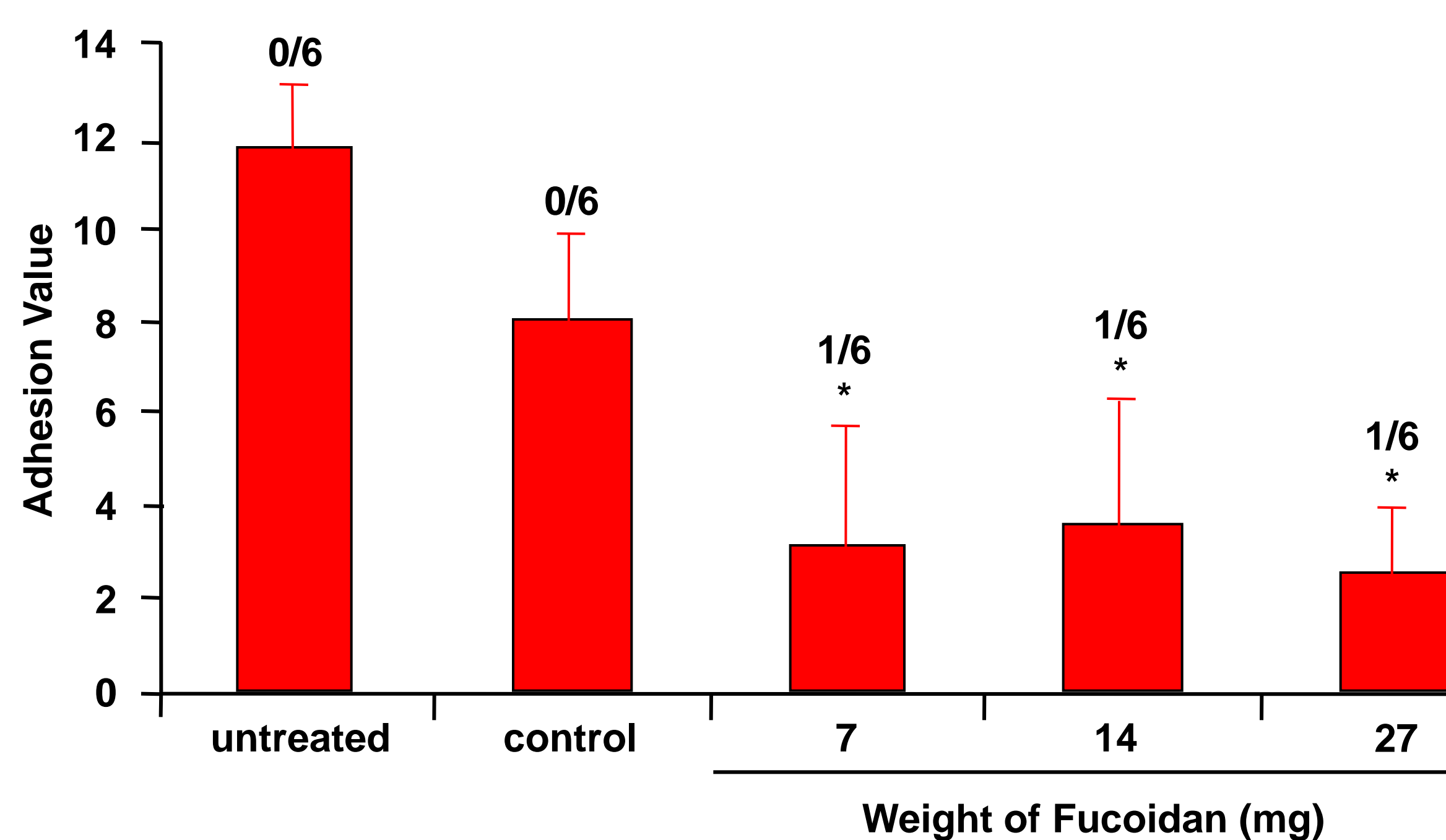


Figure 3. Effect of varying fucoidan load in fucoidan gel on adhesion formation between the caecum and the peritoneal sidewall of rats following caecal-sidewall surgery. The fractions given above each treatment group bar represent the number of animals that were found to have no adhesions, over the number of animals in each treatment group. Data represent the mean Adhesion Value ± standard deviation of 6 animals per group. * Statistically significant compared with untreated and control gel (Students' t-test, $p < 0.05$).

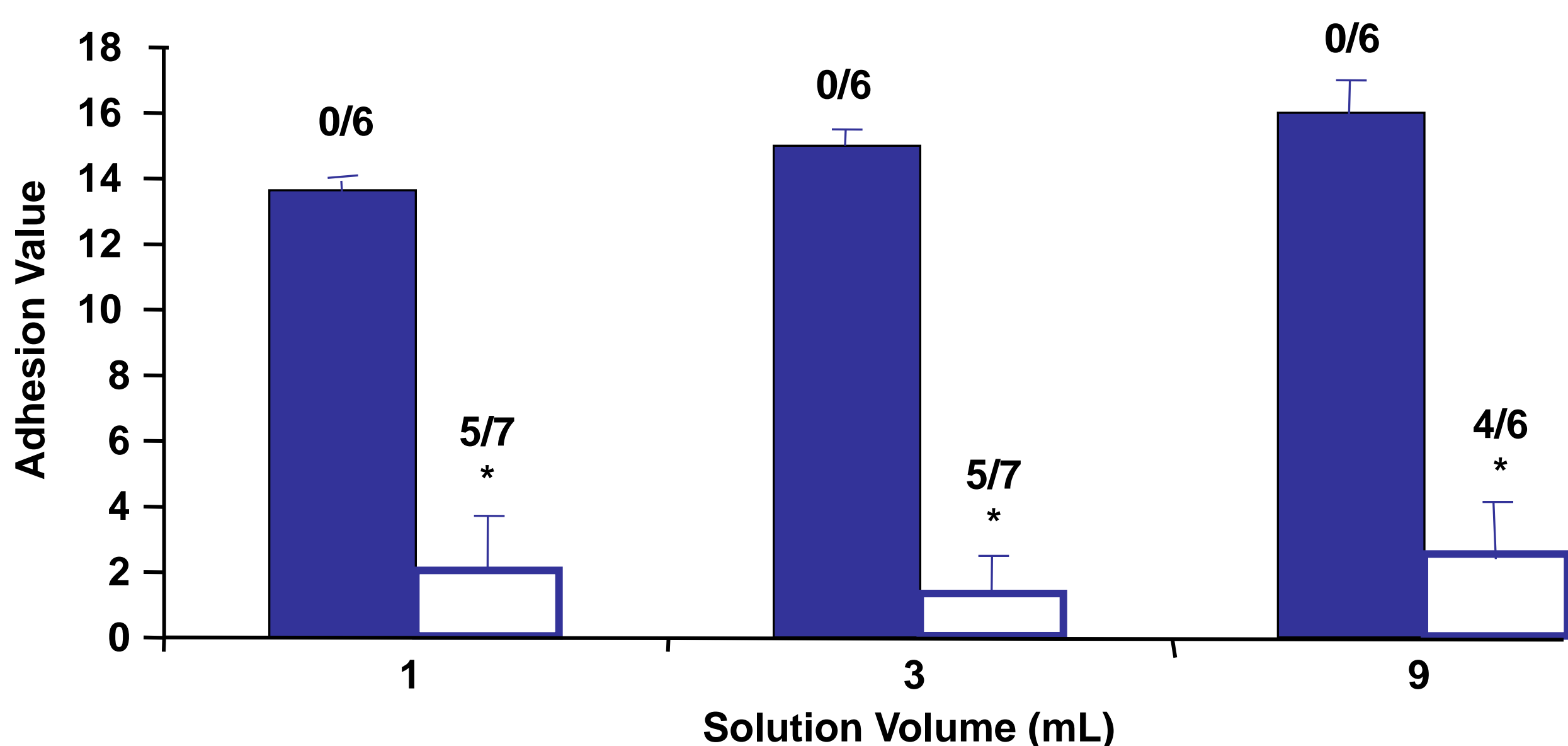


Figure 5. Effect of varying volume of fucoidan solution (□) and LRS (■) on adhesion formation between the uterine horn and the peritoneal sidewall of rats following uterine horn and sidewall surgery. Each fucoidan solution contained a total of 0.15 mg of fucoidan. The fractions given above each treatment group represent the number of animals with no adhesions, over the total number of animals in each treatment group. Data represent the mean Adhesion Value ± standard deviation of 3 (LRS group) or 6-7 (fucoidan solution group) rats. * Statistically significant compared to corresponding control (Student's t-test, $p < 0.05$).

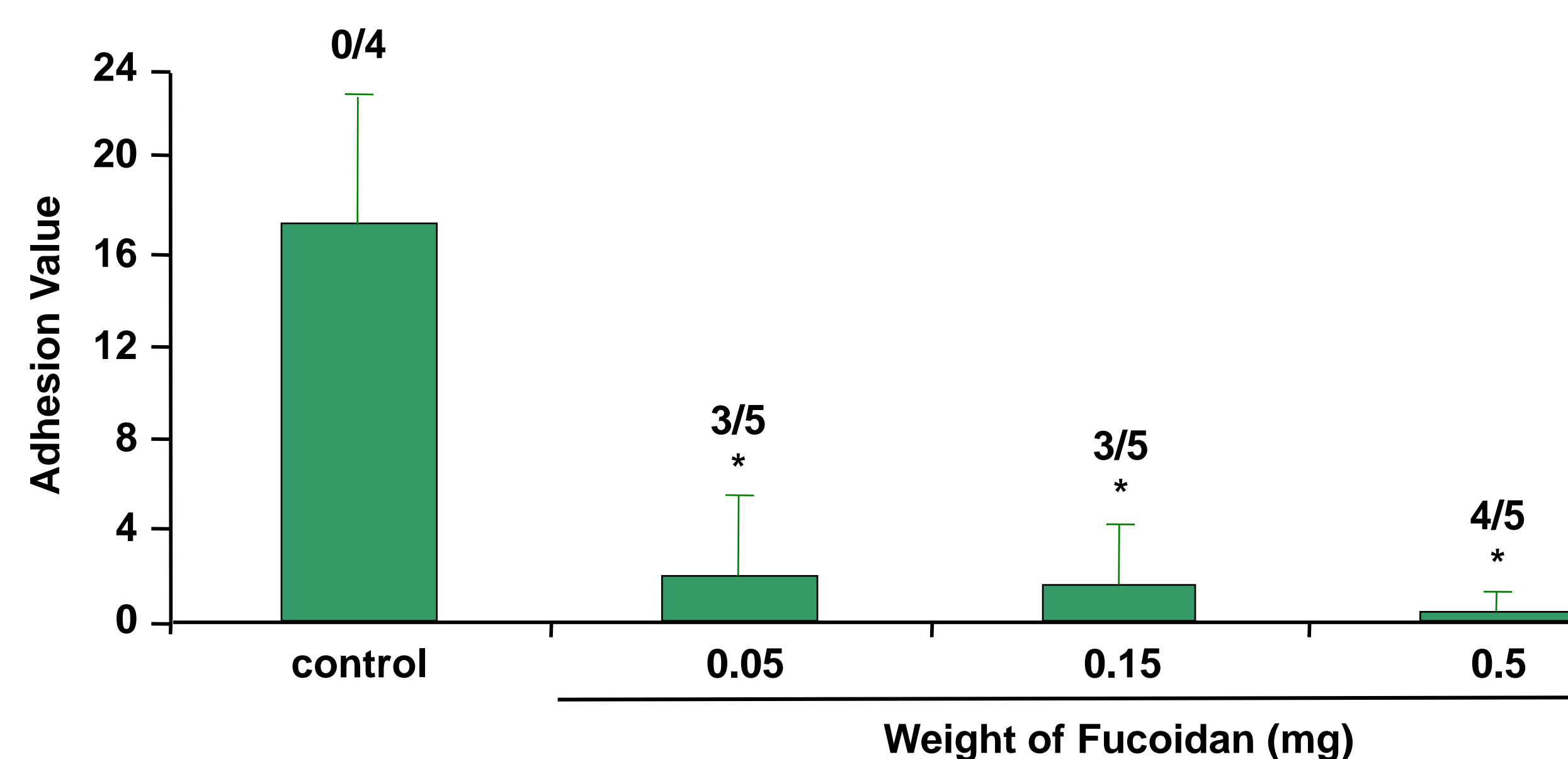


Figure 7. Effect of varying fucoidan load in fucoidan solution on adhesion formation between the uterine horn and the peritoneal sidewall of rats following uterine horn and sidewall surgery. The fractions given above each treatment group bar represent the number of animals that had no adhesions, over the number of animals in each treatment group. Data represent the mean Adhesion Value ± standard deviation of 4-5 animals. * Statistically significant compared to corresponding control (Student's t-test, $p < 0.05$).

CONCLUSIONS

- Fucoidan gel and fucoidan solution were easily and safely administered during caecal-sidewall and uterine horn-sidewall surgeries in rats.
- Fucoidan gel resulted in a 54 to 74% reduction in adhesion score and an increase from zero to 17% of animals being adhesion free.
- Fucoidan solution resulted in an 84 to 98% reduction in adhesion score and an increase from zero to 60 to 80% of animals being adhesion free.
- Fucoidan gel and fucoidan solution are promising candidates for the reduction of adhesion formation in laparoscopy and laparotomy procedures.

Table 1. Effect of varying fucoidan load in fucoidan gel on adhesion formation and safety parameters seven days following the caecal-sidewall surgical procedure. White blood cell (WBC) and change in weight data represent the mean ± standard deviation.

Weight of Fucoidan (mg)	Animals Without Adhesions (%)	WBC ($\times 10^7$)		Change in Initial Weight (%)
		Day 0	Day 7	
Untreated	0	1.0 ± 0.5	0.6 ± 0.3	17.3 ± 3.7
Control	0	0.8 ± 0.3	0.9 ± 0.6	19.4 ± 5.2
7	17	0.8 ± 0.3	0.7 ± 0.4	17.4 ± 3.3
14	17	1.0 ± 0.4	0.8 ± 0.1	15.9 ± 2.8
27	17	1.2 ± 0.4	0.7 ± 0.4	15.1 ± 2.8

Table 2. Effect of varying volume of fucoidan solution and LRS on adhesion formation and safety parameters seven days following the uterine horn-sidewall surgical procedure. White blood cell (WBC) and change in weight data represent the mean ± standard deviation.

Weight of Fucoidan (mg)	Treatment Volume (mL)	Animals Without Adhesions (%)	WBC ($\times 10^7$)		Change in Initial Weight (%)
			Day 0	Day 7	
control	1	0	1.1 ± 0.4	0.6 ± 0.0	8.3 ± 1.6
control	3	0	1.2 ± 0.0	0.8 ± 0.5	7.1 ± 4.3
control	9	0	0.9 ± 0.1	0.9 ± 0.5	0.3 ± 5.5
0.15	1	71	1.1 ± 0.3	0.8 ± 0.2*	3.5 ± 5.2

Table 3. Effect of varying fucoidan load in fucoidan solution on adhesion formation and safety parameters seven days following the uterine horn-sidewall surgical procedure. White blood cell (WBC) and change in weight data represent the mean ± standard deviation.

Weight of Fucoidan (mg)	Animals Without Adhesions (%)	WBC ($\times 10^7$)		Change in Initial Weight (%)
		Day 0	Day 7	
Control	0	1.0 ± 0.1	1.0 ± 0.1	0.0 ± 2.6
0.05	60	0.9 ± 0.3	0.6 ± 0.2	-1.5 ± 4.1
0.15	60	1.1 ± 0.3	0.9 ± 0.3	1.1 ± 3.7
0.3	80	1.3 ± 0.1	1.0 ± 0.4	3.0 ± 1.8

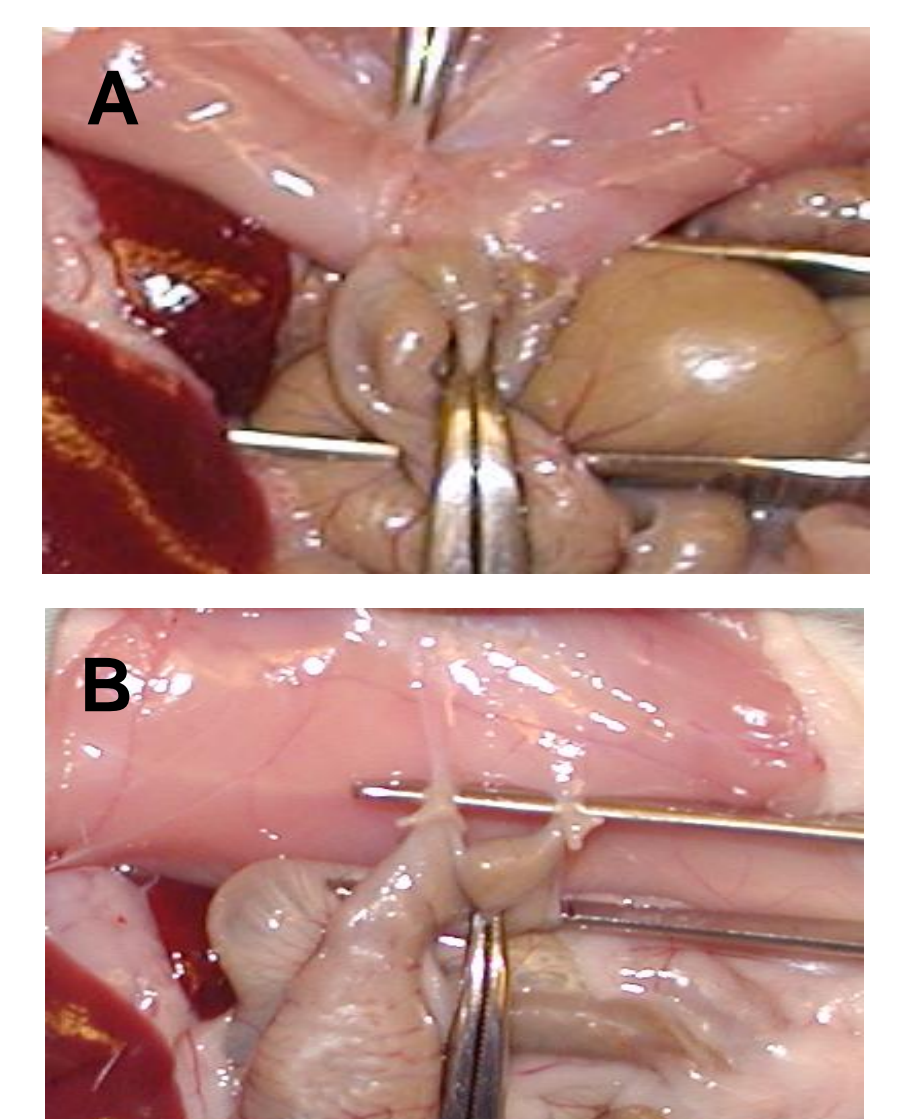


Figure 4. Photographs of the surgical site in rats 7 days after the caecal-sidewall procedure. (A) untreated and (B) fucoidan gel treated rats with adhesion scores of 12 and 0, respectively.

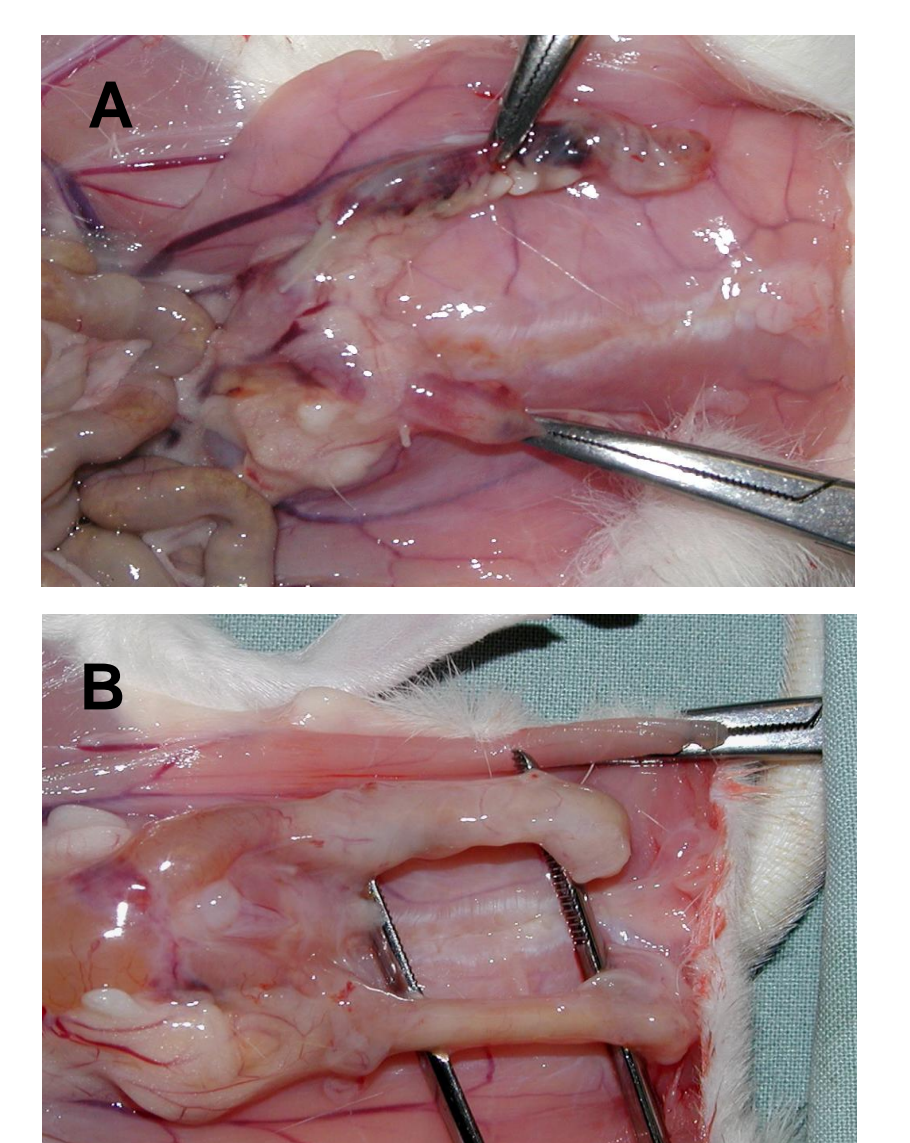


Figure 6. Photographs of the surgical site in rats 7 days after the uterine horn-sidewall procedure. (A) 3 mL control solution and (B) 0.15 mg in 3 mL fucoidan solution treated rats with adhesion scores of 16 and 0, respectively.

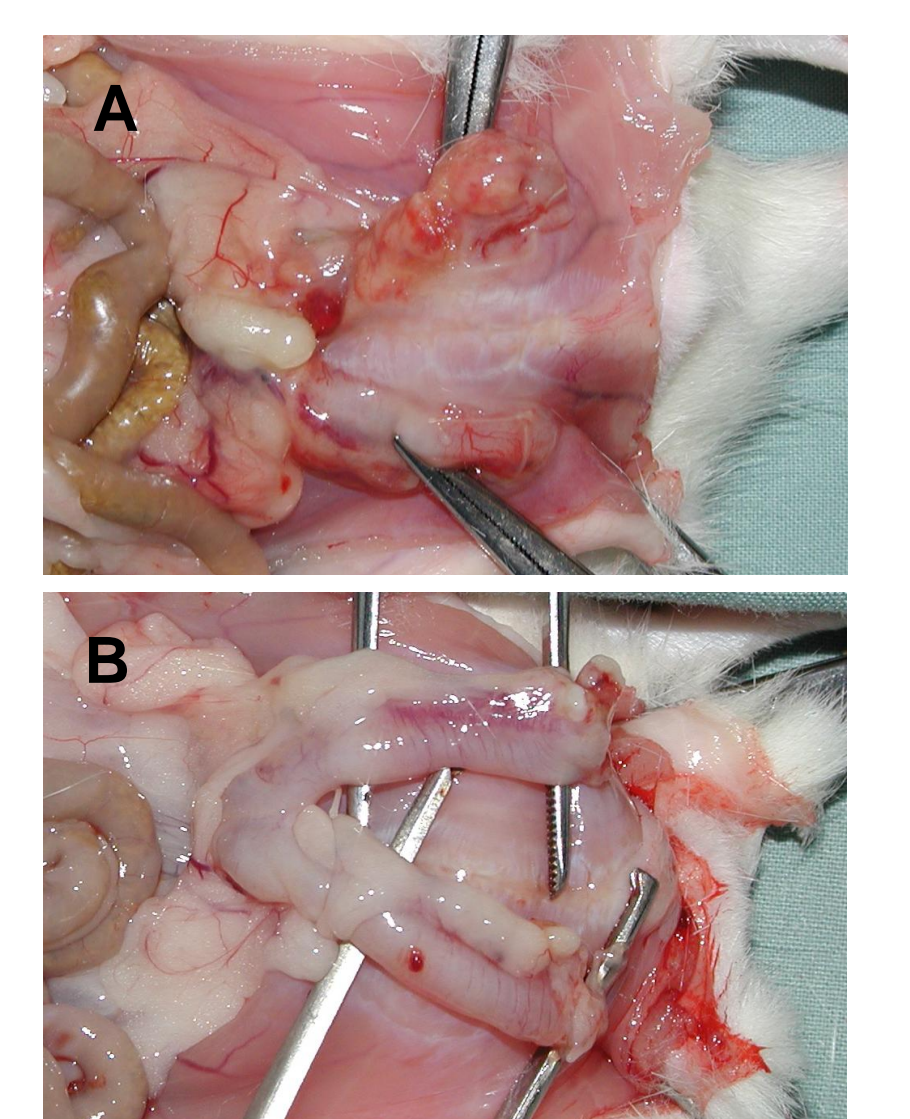


Figure 8: Photographs of the surgical site in rats 7 days after the uterine horn-sidewall procedure. (A) control and (B) fucoidan instillate (0.05 mg) groups are shown with adhesion scores of 24 and 0, respectively.