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The effect of a free peritoneal patch on bursting pressure in primary colonic anastomosis with intraperitoneal infection conditions (Study in New Zealand Rabbit)

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***Abstract*---**Anastomotic leakage following colorectal resection is reported to have a significant mortality and morbidity. Various surgical technologies have been developed to improve the outcome of colonic anastomotic, including biomaterial protective agent which has limitations in expensive price and rejection risk. The free peritoneal graft contains growth factors, antimicrobial agent and progenitor or stem cell nature by Mesothelial-Mesenchymal transition mechanism for wound healing process. Examining the healing of colonic anastomotic treated with free peritoneal graft in the presence of intraperitoneal infection by measuring the bursting pressure of the colonic tissue after surgery. We conducted an experimental study using 30 fecal peritonitis-induced New Zealand White Rabbit in 2 sample groups. Both of them have half circumferential diameter colonic resection treated with primary anastomotic using 5/0 silk braided suture material. In the treatment group, free peritoneal auto-graft was harvested and applicated. Bursting pressure was measured on the colonic tissue treated with anastomosis on day-7. The changes in the rabbits' body weight before and after surgery which describe the nutritional status did not significantly affect the bursting pressure value (P = 0.745). Importantly, we found that the bursting pressure of group treated with free peritoneal graft was significantly higher than

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the control group treated without free peritoneal graft (P = 0.001). Free peritoneal graft can be used to prevent anastomotic leakage in intraperitoneal infection condition, showed by higher bursting pressure value of colonic tissue in the surgical site.

***Keywords*---**free peritoneal patch, bursting pressure, primary colonic anastomosis, intraperitoneal infection.

Introduction

Anastomotic leaks are one of the consequences of gastrointestinal anastomoses that increases the risk of morbidity and death, has an impact on oncological outcomes, and consumes hospital resources. Anastomotic leaking following colorectal resection has been linked to a high risk of death (6–22%). Patients with anastomotic leak have a much higher morbidity rate, which leads to reoperation, interventional radiology, and a permanent stoma (Vermeer TA et al, 2016).

Anastomotic leak has a number of risk factors, both local, operative technique and systemic. The leakage rate increases up to 2.5 times in cases of colonic anastomotic resection with peritonitis. Bacterial peritonitis is a risk factor for anastomotic leaking in the short term (De Hingh IHJT et al, 2003). In colorectal surgery, the inversion approach of clipped bowel angles has a lower risk of leakage than the eversion technique (8% vs. 43%, respectively) (Goligher JC et al, 1970). Eversion type anastomoses exhibit higher rates of leakage and adhesion development in investigations with experimental animal models (Abramovitz HB et al, 1971).

Wound healing in peritonitis can be aided by MMP activity. Furthermore, fibroblasts work to replace the previously damaged tissue matrix with granulation tissue that contains many collagens during the wound healing process. Collagen will be generated by smooth muscle cells and fibroblasts in the submucosal layer during the proliferative phase, which will be lysed by collagenase activity (Witte MB, 2003). After intestinal anastomosis, collagen synthesis peaks on days 5 to 7, and the strength of the anastomosis is strongly dependent on the amount of collagen present at that time.

The mechanical success of the anastomosis will be determined using two types of measurements: tensile strength (breaking strength) and bursting pressure (bursting strength). Bursting pressure measures are used to assess the anastomosis' overall integrity, or the intestinal wall's resistance to increased intraluminal pressure. Within 7 days of the anastomosis, the bursting pressure will reach its peak (Thompson SK et al, 2006;Khoorjestan SM et al, 2015).

Due to its lack of vascularity, the free peritoneal graft (FPG) was previously considered unsuitable for the repair of large holes in the bowel wall or anastomoses. In another study, FPG as a graft in a defect that only leaves the mucosa received sufficient blood supply from the injured intestine, similar to the Split Thickness Skin Graft (STSG). The lack of commonly used biomaterials such as dry amniotic membranes and fibrin glue, as well as the source of collagen in

the parietal peritoneum, raises the question of whether peritoneal autograft can be used to help heal intestinal anastomotic wounds, especially in peritonitis conditions that cause excessive MMP and interfere with wound healing.

Because the anatomical structure and histology of the intestines are similar to humans, we conducted study on the New Zealand White Rabbit. The use of Free Peritoneal Graft as a wound barrier (sealant) on intestinal anastomoses, which contains collagen and is expected to develop into fibroblasts. We aimed to investigate the effect of free peritoneal graft as a biologic dressing on left colon anastomoses experimentally under conditions of intraperitoneal infection reflected by the burst pressure of the anastomotic site.

Materials and Methods

Study design and animal model

This is an experimental study using New Zealand rabbits in a real experimental study design. The research was carried out on New Zealand rabbits, which have a comparable anatomical structure to humans in the abdomen, liver, and intestines. The digestive system's anatomy, physiology, and biochemistry are comparable to that of humans. At the conclusion of the investigation, variable measures were taken. The rabbit used in this study were aged 6-9 months old rabbit from the experimental animal unit and weighing between 1,900 and 2,500 grams. In total, we utilized a total of 30 New Zealand White Rabbits to be included in this study. This study was reviewed and approved by an ethical clearance from the Research Ethics Commission / Animal Care and Use Committee (ACUC) Faculty of Veterinary Medicine, Airlangga University.

Anastomosis technique and burst pressure measurement

Simple randomization was used for randomization. We divided the entire 30 New Zealand rabbits into two groups, consisted of 15 rabbits in each group. The first group was given simple interrupted sutures and the other was given a simple interrupted sutures with free peritoneal patch. Each rabbit is given a number that is tattooed on its ear. The experiment was performed in the Animal Research unit Laboratory, Airlangga University (Surabaya, Indonesia). We performed fecal-induced peritonitis to all of the rabbits by injecting a fecal solution intraabdominal (doses of 4 mg/kg body weight). The anastomosis was done one day after peritonitis induction. All the surgical procedure was done by same operator to ensure consistency. The first group was treated with simple interrupted suture technique with free peritoneal patch to seal the anastomotic site, while in the other group we only used simple interrupted suture technique for anastomosis.

The burst pressure was measured 7 days after surgical procedure. We resected the anastomosis site and then performed the bursting pressure measurement using a syringe (Terumo syringe pump TE-331) 1 ml/minute connected with manometer (Nova Presameter, Riester). The bursting pressure was then recorded for further analysis.

Statistical analysis

Data analysis was carried out using SPSS 16 software (IBM Statistics, USA). The results from the study were then recorded and analyzed using the Saphiro-Wilk test for normality test. If the data were normally distributed (p> 0.05), a paired t-statistic test was used to evaluate how different the two groups were. If the data were not normally distributed, the Wilcoxon statistical test was used to determine whether the two groups differed. The P value of less than 0.05 was considered significant.

Discussion

Sample characteristics

This experiment was carried out on 30 male New Zealand White Rabbit rabbits, aged 6-9 months and weighing between 1900 and 2500 grams. The research participants were chosen from the same birthplace, nurtured in the same environment, and fed the same food both before and after surgery. To avoid bias, all procedures were performed blindly by the same surgical operator. In some rabbits of all groups, intraabdominal instillation of the rabbit' fecal sample was followed by clinical signs of peritonitis 24 hours after induction such as chromodacyorrhea, hunched position, pilierection and diarrhea. These findings were related to the sepsis condition.

There were no dead samples in the two experimental animal groups, the control group and the treatment group utilizing the free peritoneal patch. There was one sample with an enterocutaneous fistula in the treatment group, resulting in 14 of 15 rabbits being tested, whereas all samples of experimental animals could be analyzed in the control group.

We analyzed the study sample's average age and body weight (Table 1) and also post-surgery body weight and length of surgery for the 30 New Zealand white rabbits (Table 2). This experiment was carried out on 30 males New Zealand White Rabbit rabbits, aged 6 to 9 months and weighing between 1900 and 2500 grams. The study participants were chosen from the same birthplace, nurtured in the same environment, and fed the same food both before and after surgery. To eliminate prejudice, all treatments were administered blindly by the same surgical operator.

Table 1. Sample Characteristics

Sample characteristics	Test group	
	Control	Control
Rabbit Age*		
Mean	7.40	7.60
Maximum	9.00	9.00
Minimum	6.00	6.00
Median	7.00	8.00
SD	0.98	0.82
Rabbit Body Weight**		

Mean	2120.00	2163.33
Maximum	2250.00	2310.00
Minimum	1950.00	1930.00
Median	2140.00	2160.00
SD	105.35	127.03

*in month
**in gram

Table 2. Characteristics of post-surgery weight and the length of operation

Parameter	Test group	
	Control	Treatment
Post-surgery weight*		
Mean	2030.67	2068.67
Maximum	2190.00	2250.00
Minimum	1850.00	1790.00
Median	2010.00	2060.00
SD	105.59	129.88
Surgery duration**		
Mean	28.26	38.20
Maximum	32.00	44.00
Minimum	25.00	34.00
Median	28.00	38.00
SD	2.15	3.36

*in Grams

**in Minutes

The average age of the experimental rabbits in the control sample group was 7.4 ± 0.98 months, while the average age of the experimental rabbits in the treatment sample group was 7.6 ± 0.82 months, according to the data analysis. The Saphiro-Wilk test was used to test the normality of the data, yielding P = 0.052 in the treatment group and P = 0.082 in the control group. This indicates that the age of the experimental rabbits in both groups has a normal distribution, and the statistical test to compare the two is a two independent t-test, with the test results on the age data of the experimental rabbits being P = 0.552, indicating that the age of the experimental rabbits in the control sample group and the treatment are not significantly different.

The weight of the experimental rabbits was also analyzed, and the average weight of the experimental rabbits in the control sample group was 2120 ± 105.35 grams, whereas the average weight of the experimental rabbits in the treatment group was 2163.3 ± 127.03 grams. The Saphiro-Wilk normality test revealed P = 0.205 in the treatment group and P = 0.166 in the control group, indicating that the weight of the experimental rabbits in the two sample groups follows a normal distribution. The statistical test to compare the two is the test Two independent t-test, which revealed P = 0.387 on the weight data of the experimental rabbits. This means that the weight of the experimental rabbits in the control and treatment groups was not significantly different.

The strength of colonic anastomoses in peritonitis is regulated by systemic, local, and surgical factors that are all engaged in wound healing. The activation of keratinocytes, fibroblasts, endothelial cells, macrophages, and platelets in wound healing is a type of biological response to tissue disturbance or injury. After achieving homeostasis, the wound will go through four phases of healing: inflammatory, epithelialization, proliferative, and maturation. In the proliferative phase, fibroblasts play an important role in tissue proliferation and collagen synthesis (Soylu S et al, 2018). The strength of colonic anastomoses in peritonitis is determined by the balance of matrix metalloproteinase-mediated breakdown and de Novo collagen synthesis (De Hingh IHJT et al, 2003).

The features of the research sample can influence the study's results in this study. To eliminate bias, the research sample was designed as homogeneous as feasible. The experimental animals were chosen from the same location (Center for Veteriner Farma) and fed the same diet. In this study, 30 rabbits were chosen and divided into two groups: 15 samples for the group that did not use Free Peritoneal Graft and 15 samples for the group that did use Free Peritoneal Graft.

Intraperitoneal infection condition of the sample used fecal induced peritonitis from rabbit fecal material. In some rabbits of all groups showed clinical signs of peritonitis in 24 hours after induction. Hematologic and clinical chemistry parameters after intrabdominal instillation of the rabbits fecal was not evaluated because of the clinical signs of peritonitis has been showed although Intraperitoneal pus was not found in some rabbits of all groups. Fecal induced peritonitis for animal research as identical as human model data which caused sepsis based on SOFA Score evaluation, inflammatory response duration from induction until host bacteremia condition is consistent although sepsis duration is not (Park I, *et al*, 2019). In septic condition there is a defect in cellular oxygen utilization, anaerobic metabolism occur and blood lactate level will increase as a result (Budipramana VS, 2021). An initial supportive therapy and parenteral broadspectrum antibiotics were prominently important to undertake while waiting for further diagnostics and therapies arrangements were made (Pranata AK, 2021). A statistical test using two independent t-tests on rabbit age and rabbit weight before surgery revealed that both were still homogeneous, indicating that differences in age and weight of rabbits before surgery did not cause bias.

Characteristics of length of operation of experimental animals

Experimental rabbits in the control sample group had an average length of operation of 28.26 ± 2.15 minutes, while experimental rabbits in the treatment sample group had an average length of operation of 38.2 ± 3.36 minutes (Table 2). The normality test of the Saphiro-wilk data revealed that the length of operation data is normally distributed (P = 0.234 in the treatment group and P = 0.285 in the control group). Two separate t-tests showed that the length of operation on experimental rabbits in the control and treatment sample groups was significantly different (P = 0.0001).

Further, we analyzed the association between each group's length of operation and bursting pressure levels to identify anastomotic leakage factor. We found that there was a significant association between the duration of operation and the

bursting pressure (P = 0.002) indicating that length of operation had effect on bursting pressure value.

There was a substantial difference in the length of operation between the two control and treatment groups, according to statistical testing using two independent tests. This is because, according to the researchers, collecting peritoneum and cleansing peritoneal tissue from linked surrounding tissues such as abdominal wall muscles and fascia took longer in the therapy group. Length of operation between the two control and treatment groups, according to statistical testing using Pearson Correlation test showed medium correlation between length of operation and bursting pressure which means length of operation correlate with clinical outcome. This correlation explained 1 sample from treatment groups who get enterocutan fistula because this sample get the longest operation time. Based on Kumar *et al* Study, enterocutan fistula is one of the anastomotic leakage complications (Kumar P et al, 2011). Operation duration is independent factor that caused anastomotic leakage which associated with complicated procedure, intra-abdominal adhesion, surgeon experience and fatigue (Park JS et al, 2016; Telem DA et al, 2010; Cheng Hang et al, 2017).

Characteristics of changes in body weight of experimental animals

We examined the characteristics of body weight of the animal model post-operatively. The average postoperative body weight of experimental rabbits in the control group was 2030.67 ± 105.59 grams, while it was 2068.67 ± 129.88 grams in the treatment group. According to the Saphiro-Wilk normality test, the post-operative body weight of the experimental rabbits in the two sample groups shows a normal distribution (P = 0.487 in the treatment group and P = 0.591 in the control group).

The two independent t-test was suggested that the experimental rabbits' post-operative body weights in the control and treatment groups were not statistically different (P = 0.318). The changes in the weight of the experimental rabbits (delta body weight) before and after treatment are analyzed and is shown in Table 3. The mean delta weight of the experimental rabbits in the control group was 89.3 ± 39.54 grams, while it was 94.67 ± 44.37 grams in the treatment group. The Saphiro-wilk normality test indicates that the delta of body weight of the experimental rabbits in the two sample groups has a normal distribution (P= 0.086 in the control group and P = 0.327 in the treatment group). Two independent t-test showed that the experimental rabbits' delta body weight in the control and treatment groups was not substantially different (P = 0.731).

Table 3. The changes in the weight of the experimental rabbits before and after treatment

Sample group	Weight change*	P-value
Control Group		
Mean	89.33	
Maximum	190.00	
Minimum	40.00	
Median	90.00	
SD	39.54	
		P = 0.731
Treatment Group		
Mean	94.67	
Maximum	190.00	
Minimum	20.00	
Median	80.00	
SD	44.37	

This implies that the rabbits got the same nutrition and cage care, resulting in no differences in postoperative nutritional status between the groups.

Comparison of Bursting Pressure Anastomosis

The experimental rabbits were killed by decapitation seven days after anastomosis surgery, immediately (Figure 1). The abdominal cavity was opened and inspected visually and a sample of intestine anastomotic tissue was collected for bursting pressure measurement (Figure 2).

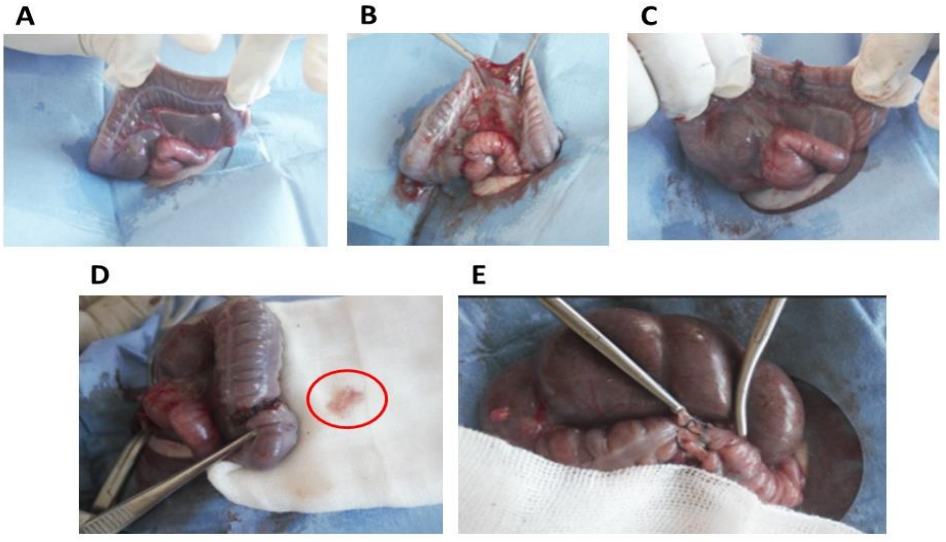

Figure 1. The effect on colonic anastomoses. (A) The segment of the colon to be treated is chosen. (B) Colon incision of full thickness. (C) anastomotic suturing, (D) harvested peritoneum (E) colonic anastomoses grafted with peritoneum

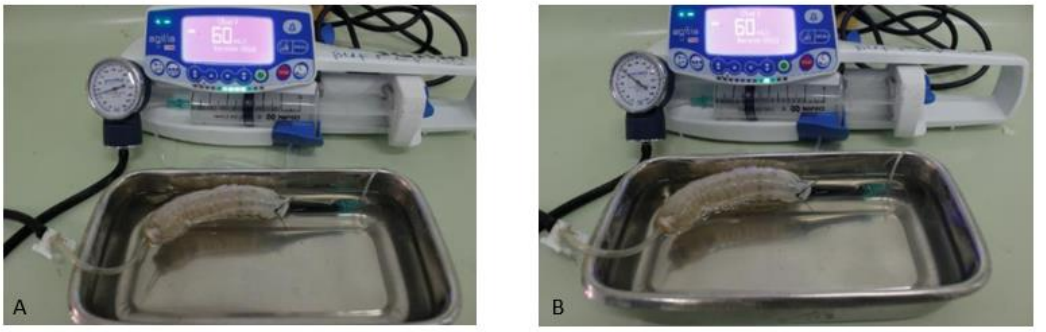

Figure 2. The bursting pressure was measured as previously described. (A) Using a syringe pump, air is injected into the colon (1 ml/minute) (B) Bursting pressure sign when the anastomosis is leaking, bubble (+).

Experimental rabbits in the control sample group had an average bursting pressure of 99.6 ± 13.54 mmHg, while experimental rabbits in the treatment sample group had an average bursting pressure of 116.80 ± 10.92 mmHg. The normality showed that the experimental rabbits' bursting pressure data in the two sample groups follows a normal distribution (P = 0.334 in treatment group and P = 0.089 in the control group). Then, to compare the two, an independent t-test is used. We found that there was a statistical difference in bursting pressure in the anastomotic group (P = 0.001) colon without free peritoneal graft and colonic anastomosis group with free peritoneal graft (Table 4).

Table 4. Comparison of Bursting Pressure Anastomosis

Sample group	Bursting Pressure Value	P-Value
Treatment Group		
Mean	116.80	
Maximum	132.00	
Minimum	90.00	
SD	10.92	P = 0.001
Control Group		
Mean	99.60	
Maximum	132.00	
Minimum	80.00	
SD	13.54	

We also analyzed the association between each group's body weight change (delta body weight) and bursting pressure levels to reduce statistical bias. The correlation analysis with the Pearson test yielded a value of P = 0.745, indicating that changes in body weight before and after surgery have no effect on each group's bursting pressure value.

In the study of intestinal anastomoses, mechanical metrics constitute an important benchmark. Bursting Pressure and Tensile Strength assessments are the two most commonly utilized assessment methods in intestinal anastomosis studies, although there is no consensus in the literature on which method is best

(Duraes L de C et al, 2013). There were significant variations in bursting pressure readings between the control and treatment groups, according to the findings of statistical comparison tests using two independent t-tests. Ex vivo (outside the abdomen) measures were used in this investigation since the results were similar to in vivo measurements as long as they were completed in less than 48 hours and stored in normal saline solution. Furthermore, both in vivo and ex vivo studies can be used in clinical trials (Watters DAL et al, 1985;Pearce SC et al, 2018). The measurements were carried out objectively by the researchers using calibrated measuring devices. In a review of 20 years of experimental colonic anastomosis healing, Raptis *et al* also stated that busting pressure is a reliable element for determining anastomotic strength, and that it is measured shortly after experimental animals are sacrificed (Raptis D et al, 2018).

Colonic anastomotic leakage is caused by a combination of risk factors, including both patient and surgical risk factors (McDermott F et al, 2016). Because emergency situations like peritonitis or sepsis can raise the likelihood of anastomotic leakage by up to 4.6 times (McDermott et al, 2016), one way to limit the risk of leakage and promote colonic anastomotic healing is to use anastomotic protection.

The patient's dietary state is one of the risk factors for intestinal anastomotic leaking. Malnutrition is an essential concern that is directly associated to postoperative patient outcomes, according to a study conducted by Young Lee *et al* in 2018. This is due to the fact that starvation can affect the immune system and the healing process of wounds. Measuring nutritional status becomes critical, and the MST (Malnutrition Screening Tool), which comprises of weight loss and reduced food consumption, is a quick screening tool (Lee SY et al, 2018). As a result, this study significant correlation between weight loss and the bursting pressure value, indicating that each group's nutritional status and consumption are same and have no effect on the bursting pressure value. This also suggests that there was no nutritional bias between the two groups.

Wound healing is a complex process that begins with disruption of tissue integrity. Various properties of the peritoneum are antimicrobial (VanBaal J et al, 2017, Padwal M et al, 2017), accelerate proliferation and provide extracellular matrix for cell migration (Zhang Q et al 2010, Bartheloot D et al, 2017), increase angiogenesis (Rout UK et al, 2002,Mutsaer SE et al, 2016) and has progenitor or stem cell properties through the Mesothelial-Mesenchymal Transition mechanism (Lopez C et al, 2014) making free peritoneal grafts one of the biological protection options for colonic anastomoses. Peritoneum used as an autograft has the advantage that in general the graft rejection rate is quite low (72-92% autograft received by recipients) compared to aulograft (45-46% received by recipients) and xenograft (33-36% received by recipients) (Almutairi AS et al, 2019).

Based on the results of this study, we found that there was a significant difference in bursting pressure between the treatment group and the control group. In this study the measurements were carried out on the seventh day and showed a higher bursting pressure on the anastomosis colon using free peritoneal graft compared to colonic anastomosis without free peritoneal graft. Clinically, it means that the group with higher bursting pressure has a better recovery and

can prevent leakage after anastomosis in peritonitis conditions. Nordentoft *et al.* conducted an experimental study on gastrointestinal anastomoses added with fibrin glue, which explained that to assess the effectiveness of additional sanitary napkins, it was not only measured by bursting pressure but also evaluated by anatomical pathology whether the intestinal wall to which the dressing was added leaked or not (Nordentoft T et al, 2007). Therefore, this study can be used as a reference value for further research, with the hope that a higher bursting pressure rate is also directly proportional to the fibroblast-collagen levels in colonic anastomoses.

The main problem associated with intestinal anastomoses is leakage. Bursting pressure in anastomoses reflects anastomotic strength and higher bursting pressure is associated with stronger anastomoses within 1 week postoperatively. Therefore, bursting pressure is considered the most important factor in assessing the quality of intestinal sutures (Kawasaki K, 2011).

The injured peritoneum will proliferate its mesothelial cells to support the proliferation process, there is also an increase in angiogenesis and an increase in the amount of extracellular matrix, which as previously known that peritonitis causes damage to the extracellular matrix so that it has an impact on collagen lysis. With the presence of this peritoneum in colonic anastomotic wounds, we suspect that the wound healing process at the anastomotic site becomes better.

Mesothelial cells in the peritoneum have the ability to transition from mesothelial to mesenchymal cells where these mesenchymal cells can become myofibroblasts and smooth muscle cells (Gronthos S et al, 2003; Rosellini A et al, 2007; Lin G et al, 2008). Mesenchymal stem cells (MSCs) are able to give rise to different cell phenotypes (Castiglione F et al, 2016). The capacity of MSCs to differentiate is not only characteristic that makes these cells appealing for therapeutic medicine (Castiglione F et al, 2016). Previous study also stated that endometrial mesothelial cells have progenitor cell properties. In intestinal anastomotic wound healing, the target of good wound healing is to balance the amount of collagen production and degradation in the intestine which is not only produced by fibroblasts but also smooth muscle cells (Faroutan T et al, 2010). We suspect that the higher value of bursting pressure in the colonic anastomosis with the addition of the free peritoneal patch is due to the higher collagen production due to the nature of the mesothelial cells in the patch.

Besides the above mechanism, Cina et al found the presence of a biological component in the peritoneum and its implications for wound healing, namely PDGF-B. In fibrogenesis, PDGF-B is generally recognized as a potent inducer and chemotaxis and mitogenic for myofibroblasts, as well as a potent stimulus for mesenchymal cell migration (Cina D et al, 2009). The presence of these growth factors and the benefits of adding a free peritoneal patch to colonic anastomoses can be taken into consideration for further research. The presence of these growth factors and the benefits of adding a free peritoneal patch to colonic anastomoses can be taken into consideration for further research. Several studies also reported increased fibroblast proliferation is associated with overexpression of extracellular matrix and Connective Tissue Growth Factor (CTGF) (Pranata FH et al, 2022)

Conclusion

There was significant relationship between the effect of a free peritoneal patch on the bursting pressure in primary colonic anastomosis with intraperitoneal infection conditions. The addition of a free peritoneal patch to the colonic anastomosis under conditions of intraperitoneal infection can give a better anastomosis result than without the free peritoneal patch seen from the higher bursting pressure value.

The limitation in this study is that intraperitoneal condition was not evaluated by objective parameter for infections such as laboratory to calculate SOFA Score and blood or peritoneal liquid culture. Nevertheless, we believe that the clinical signs of peritonitis may represent the measurement of the intraperitoneal conditions that is also supported by previous study explanation.

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