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Comparison of Inflammation, Pain, and Recovery in Colorectal Cancer Patients Undergoing Surgery with General Anesthesia and Combined Epidural

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Abstract

Colorectal cancer has a high incidence and mortality rate. Surgery can increase the cytokine IL-6 which triggers inflammation and metastasis. The combination of general and epidural anesthesia has the potential to suppress IL-6, improve the tumor microenvironment, provide analgesia and improve postoperative recovery. To compare the effectiveness of postoperative analgesia quality in colorectal cancer patients receiving general anesthesia with combined epidural anesthesia. The single blind RCT study involved 44 patients who underwent surgery on colorectal cancer at Prof. Ngoerah Hospital. The study subjects were divided into two groups, group K who received general anesthesia and group P who received general anesthesia combined with epidural anesthesia. Patients' IL-6 will be evaluated preoperatively and 6 hours postoperatively. VAS and QOR-15 will be assessed 24 hours postoperatively. Of the 44 patients analyzed, the combined general anesthesia with epidural anesthesia group showed a significantly lower difference in IL-6 levels compared to the general anesthesia alone group of -14.69 [95% CI, p = <0.001]. The 24-hour postoperative VAS score was significantly lower than conventional general anesthesia, both in stationary and mobile conditions. In postoperative recovery, it was found that conventional general anesthesia combined with epdiural anesthesia gave greater QOR-15 results compared to conventional general anesthesia. General anesthesia combined with epidural anesthesia in colorectal cancer patients undergoing surgery can provide a lower difference in IL-6, lower VAS and higher QOR-15 postoperative satisfaction than the general anesthesia group.

Introduction

Cancer is still a problem that often occurs in the world, one of which is colorectal cancer (Sulastri, 2024). One of the abilities of cancer that is still difficult is the ability to continue to proliferate to cause metastasis to other areas of the body besides the primary local site of cancer growth. Management of colorectal cancer often requires surgical procedures which are also a factor in the occurrence of micrometastasis (Rudiman, 2023; Chandra et al., 2021; Carconi e al., 2023; Kenzi et al., 2025). In surgical procedures, anesthesia also affects this occurrence. Anesthetic drugs such as opioids are associated with supporting cancer growth by suppressing the body's immune response to cancer However, the mechanism of action of opioids and opioid receptors in the immune system is still not clearly understood (Rahardjo et al., 2020; Malafoglia et al., 2022; Lim, 2021; Bettinger & Friedman, 2024; Paul et al., 2021). The use of epidural anesthesia with local anesthetics is said to reduce the use of opioids so that it is thought to

improve the microtumor environment, one of which suppresses the inflammatory response of the cytokine Interleukin-6. In addition, epidural anesthesia also acts as a good analgesic and can improve the quality of recovery in patients with colorectal cancer undergoing surgical procedures (Guay et al., 2016; El-Boghdadly et al., 2022; Tang et al., 2024; Zhang et al., 2023).

According to Xi & Xu (2021) , colorectal cancer has caused 1.9 million cases and 0.9 million deaths worldwide. This cancer is usually found in patients aged 50 years and above (Rawla et al., 2019) . From Sehat Negeriku data, it is known that colorectal cancer is in third position covering 8.6% of all cancers that occur in Indonesia (Rokom, 2022). Management of colorectal cancer often involves surgical procedures, but surgery can cause post-surgical pain and affect the quality of recovery. In addition, the incidence of cancer recurrence and metastasis after surgery is still common and a matter of concern. Despite successful resection, postoperative cancer may recur in one-third of patients and is often metastatic and ultimately the cause of death. The inflammatory response to surgery, hypothermia, blood transfusion, tissue hypoxia, hyperglycemia and postoperative pain can create a condition of relative immunosuppression that can promote tumor growth, thus increasing the risk of metastatic recurrence. In addition to the surgery itself, the anesthetic technique and drugs used also affect this (Benish & Ben-Eliyahu, 2010; Ramirez et al., 2023). Surgery and anesthesia techniques are influential in shaping the microenvironment suitable for tumor growth through the release of hormonal mediators such as catecholamines and prostaglandins as well as cytokines such as interleukin-4 (IL-4), interleukin-10 (IL-10), *transforming growth factor-beta* (TGF-β) and the influential interleukin-6 (IL-6). Cytokine IL-6 is known to be the cytokine that plays the most role in supporting tumor growth by promoting proliferation and preventing apoptosis in tumor cells. This cytokine is one of the key cytokines that drive proliferation and metastasis in colorectal cancer (Atmaja et al., 2024; Wahyuni et al., 2024).

Anesthetic techniques and drugs play a role in influencing the microtumor environment. The choice of anesthesia with a combination of regional such as peripheral nerve block and neuroaxial such as epidural was found to improve the microtumor environment and reduce the increase in IL-6. Several studies of general anesthesia compared with epidural combination general anesthesia gave statistically lower values of IL-6 increase in combination general anesthesia with epidural anesthesia. In epidural local anesthesia given has several mechanisms that are proposed to suppress tumor cells by activating tumor suppressor genes, inhibiting tumor migration pathways, preventing differentiation and proliferation, anti inflammation by inhibiting IL-6 increase, reducing the stress response to surgery with sympathetic blockade, and increasing immune cells (Elsayed et al., 2020; Yang et al., 2024; Santander Ballestín et al., 2022).

Epidural anesthesia techniques and the use of local anesthetic drugs in some studies are found to have advantages in preventing recurrence and metastasis, but there are also some studies that provide contradictory results. In the study Hasselager et al. (2022) which assessed the effect of epidural analgesia and its relationship with recurrence in cancer, it was found that there was no relationship between epidural analgesia and recurrence. The next challenge in anesthesia in cancer patient surgery is managing postoperative pain. Postoperative pain delays mobilization and oral intake after surgery, and increases the risk of chronic postoperative pain. *The Enhanced Recovery after Surgery* (ERAS) guidelines for colorectal *surgery* recommend the use of multimodal analgesia that reduces the use of Opioids, with Paracetamol as a basic component, combined with epidural analgesia after surgery (Raharjo et al., 2022; Huang et al., 2024; Grossi, 2025). Postoperative pain should also be a concern as it will impact on patient satisfaction and postoperative recovery.

Post-surgery, satisfaction and recovery are the benchmarks that must be considered, so this is a challenge in itself. Sympathetic nerve and spinal cord block through epidural anesthesia plays a role in reducing surgical stress response, increasing blood flow to the intestines, improving

peristalsis, and providing good analgesia effect. Based on this theory, the combination of epidural block and general anesthesia is considered a key component in the rapid recovery approach in colorectal surgery. Combining these two anesthetic techniques can reduce stress response, inhibit the transmission of pain stimuli, reduce opioid use, accelerate the recovery of gastrointestinal function, and reduce the incidence of ileus, which overall accelerates recovery and shortens the duration of hospitalization. However, the quality of postoperative recovery in terms of the physical and psychological state of patients with this anesthesia protocol is not fully understood. We hypothesize that the combination of epidural block with general anesthesia may improve the quality of postoperative recovery as measured directly by patients (Liu et al., 2020; Thepsoparn et al., 2022; Zheng et al., 2023; Héroux et al., 2023).

Based on the above article, the authors aim to strengthen the results of previous studies which state that the combination of general anesthesia and epidural anesthesia techniques can improve the tumor microenvironment, reduce stress response or inflammation, and reduce postoperative pain compared to the use of conventional general anesthesia techniques. This study aims to compare the effectiveness of postoperative analgesia quality in patients undergoing colorectal cancer surgery with general anesthesia technique compared with epidural anesthesia combination technique. Specifically, this study aims to compare Interleukin-6 (IL-6) levels, Visual Analogue Scale (VAS) scores, and postoperative Quality of Recovery score (QoR-15) in both groups of patients. The results of this study are expected to provide information on anesthesia techniques that are more effective in improving the quality of postoperative recovery.

Methods

This study is a clinical trial with randomization allocation, single blind, and pre- and post-test control group design. Subjects will be divided into two groups, first the control group, which receives conventional general anesthesia techniques and the treatment group, which is general anesthesia with a combination of epidural anesthesia. Randomization is carried out to determine the placement of subjects in the treatment or control group, so that each subject has the same chance of getting into one of the groups. Single blinding in this study was the researcher himself due to the nature of the intervention (Epidural catheter insertion and postoperative intravenous analgesic drug administration).

This study was conducted in the operating room of the Central Surgical Installation of Ngoerah Hospital during the study period which lasted from December 2024 - January 2025. The study population was all patients diagnosed with cancer of the colorectal region and undergoing laparotomy surgery at Ngoerah Hospital during the period December 2024 to January 2025, until the minimum sample size was met. The study sample was taken from the affordable population using consecutive sampling technique, in which subjects who met the research criteria were selected based on the order of arrival until the required number of samples was reached. The sample size used was 44 samples, which was determined through various calculations, including changes in pre-operative and postoperative Interleukin-6 levels and 24-hour postoperative recovery quality based on the QoR-15 score, with the largest calculation result of 44 samples.

Research Procedure

Prior to the study, the researchers submitted *ethical clearance* to the ethics committee of the Faculty of Medicine, Udayana University until it was declared feasible. Furthermore, the researchers applied for a research permit to the research and development department of the Faculty of Medicine, Udayana University and to the Diklit of Ngoerah Hospital, as well as to the Department of Anesthesiology and Intensive Therapy of Ngoerah Hospital. Selection was done at the time before surgery. Patients who met the selection criteria were designated as the sample population. After receiving an explanation and the patient agreed, they signed *informed*

consent and became research subjects who met the eligibility criteria. Subjects were then randomly allocated into two groups equally, with group K as the control group receiving coventional general anesthesia and group P receiving combined general anesthesia with epidural anesthesia.

Patients will receive an explanation of the purpose of the study, the *QoR-15* questionnaire, and how and when to complete the questionnaire. Patients were recorded before anesthesia, such as patient demographic data including age, gender, BMI, ASA physical status, and treatment room. In the preparation room, midazolam 1 mg intravenously was given as premedication. In the operating room, non-invasive monitoring devices such as *sphygmomanometer*, electrocardiography, and *pulse oximetry* were installed. STATICS were set up. The patient was given oxygen via nasal cannula at 2 liters per minute. Blood was drawn for pre-operative Interleukin-6 (IL-6) examination. If *Serious Adverse Events* (SAEs) occur during the procedure or study, they will be managed to completion and reported to the anesthesiologist in charge of the patient within 24 hours.

Data analysis in this study included descriptive analysis, normality test, homogeneity test, and mean comparison analysis. Descriptive analysis was conducted to describe the characteristics of subjects and research variables based on treatment groups. Variables with numerical-ratio data scales, such as age (years) and weight (kg), were summarized using mean and standard deviation if normally distributed, or using median and interquartile range if not normally distributed. Variables with categorical data scales were presented as relative frequencies, counts, or percentages. The results of descriptive analysis were displayed in a cross-distribution table to assess the comparability of subjects between treatment groups. Normality tests were used to assess the data distribution of numerical variables, such as pain scores, pre-operative and 6-hour postoperative IL-6 levels, and postoperative recovery satisfaction scores, with the Shapiro-Wilk test because the number of samples was less than 50 per group. If the data were normally distributed, the analysis continued with a homogeneity of variance test using Levene's test to assess the uniformity of variance between groups. Furthermore, the mean comparison test was used to compare pain scores, IL-6 levels, and recovery satisfaction scores between treatment groups. Independent T-test was used if the data were normally distributed in both groups, while the non-parametric Mann-Whitney Test was used if one or both groups were not normally distributed. The entire statistical analysis process was performed using SPSS software.

Result and Discussion

In this study, there were 44 subjects who underwent surgery on patients with colorectal cancer. From the randomization results, there were 22 subjects in group K as the control group who received conventional general anesthesia and 22 subjects in group P as the treatment who received conventional general anesthesia combined with epidural anesthesia. The observed subject characteristics include categorical variables, namely gender, ASA physical status and numerical variables, namely age, BMI and SGA (Subjective Global Assessment) nutritional status. Relationships of categorical variables were analyzed using cross tabulation as well as Chi- Square. Normality in numerical variables was analyzed using the Shapiro-Wilk test, and the results were found to be non-normally distributed ($p<0.05$), so it was continued with the Mann-Whitney Test (table 5.1) to determine whether there was a significant difference in these variables between the two intervention groups.

Table 1. Demographic Characteristics of Research Subjects

Characteristics	**Intervention Group**		***P-value***
	K (n=22)	**P (n=22)**	
Age (years), median (IQR)	57 (15)	53 (17)	0,464*
Gender (%)			0,763†

Male	11 (50)	12 (54,5)	
Female	11 (50)	10 (45,5)	
BMI (kg/m^2), median (IQR)	22.65 (1,68)	22,7 (5,93)	0,906*
SGA (%)			0,55 †
A	0 (0)	0 (0)	
B	20 (90,9)	21 (95,4)	
C	2 (9,1)	1 (4,6)	
ASA Physical Status (%)			0,761†
ASA I	0 (0)	0 (0)	
ASA II	13 (59,1)	12 (54,5)	
ASA III	9 (40,9)	10 (45,5)	

Source: Data Processed by Researchers, 2025

**Mann-Whitney test*; †*Pearson Chi-Square* test. Numerical variables are shown as median (IQR) and categorical variables are shown as n (%). A value of $p<0.05$ was designated as significant.

The results showed that there was no significant difference between the intervention group (K) and control group (P) in the demographic characteristics of the study subjects. Based on the Mann-Whitney test, there was no significant difference in age (median 57 years in group K and 53 years in group P, p = 0.464) and BMI (median 22.65 kg/m² in group K and 22.7 kg/m² in group P, p = 0.906). In addition, the Pearson Chi-Square test showed that gender and nutritional status (SGA) showed no significant differences between the two groups (p = 0.763 and p = 0.55, respectively). The distribution of ASA physical status in the two groups was also not significantly different, with the majority of subjects being in ASA II (59.1% in group K and 54.5% in group P) and ASA III (40.9% in group K and 45.5% in group P). Based on these results, it can be concluded that the demographic characteristics between the two intervention and control groups are relatively homogeneous, allowing for further analysis of other research variables.

Comparison of Delta IL-6 Values in Both Groups

This study evaluated delta IL-6 by calculating the difference between pre-operative IL-6 levels and IL-6 levels at 6 hours postoperatively in both groups. Normality test was performed using *Shapiro-Wilk*, and the results showed normal distribution of delta IL-6 data. Next, *independent t-test* analysis was performed to evaluate the significance of the difference between the two groups.

Table 2. Comparison of Pre-operative and First 6 Hours Postoperative IL-6 Levels

Intervention	**Variables**			
	Pre-operative IL-6 (ng/L), Mean (± SD)	Postoperative IL-6 (ng/L), Mean (± SD)	Delta IL-6 (ng/L), Mean (± SD)	*Mean Difference* [IK95%]
Group K Conventional general anesthesia (n=22)	20.03± 5.83	61.01± 11.87	40.97± 12.85	-14,69 [(-21,55) - (-7,83), p = <0,001]‡
Group P Conventional general anesthesia combined with epidural anesthesia (n=22)	17.23± 6.68	43.51± 7.41	26,28± 9,44	

‡*independent t-test*

Source: Data Processed by Researchers, 2025

Table 2 above shows the comparison of il-6 levels pre-operatively and the first 6 hours postoperatively. Data are displayed in the form of mean and standard deviation. In group K, IL-6 levels were obtained with a mean of 20.03 with a standard deviation of± 5.83, while IL-6 6 hours postoperatively obtained a mean of 61.01 with a standard deviation of± 11.87. In group P, IL-6 levels were obtained with a mean of 17.23 with a standard deviation of± 6.68 while IL-6 6 hours postoperatively obtained a mean of 43.51 with a standard deviation of± 7.41. Thus, it can be seen an increase in the average postoperative IL-6 level 6 hours in both groups, but it is better at IL-6 6 hours postoperative in group P.

Table 3. Comparison of Delta IL-6 in Both Groups

Intervention	Variables	
	Delta IL-6 (ng/L), Mean (± SD)	***Mean Difference* [IK95%]**
Group K Conventional general anesthesia (n=22)	40.97± 12.85	-14,69 [(-21,55) - (-7,83), p = <0,001]‡
Group P Conventional general anesthesia combined with epidural anesthesia (n=22)	26,28± 9,44	

‡*independent t-test*

Table 3 above shows the comparison of delta IL-6 between the two groups. The postoperative delta IL-6 value in group K averaged 40.97 with a standard deviation of± 12.85 and postoperative delta IL-6 in group P was obtained with a mean of 26.28 with a standard deviation of± 9.44. Based on the results of statistical analysis for delta IL-6, there was a significant difference between the mean delta IL-6 of group K and group P with a value of p = 0.001 (p < 0.05). Thus, the group that received conventional general anesthesia combined with epidural anesthesia had significantly lower delta IL-6 levels of -14.69 (95% CI: -14.69 [(-21.55) - (-7.83), p = <0.001]) compared to conventional general anesthesia alone within 6 hours postoperatively.

Comparison of Recovery Quality with QoR-15 Questionnaire in Both Groups

In this study, the 24-hour postoperative recovery quality assessment was assessed based on the QoR-15 questionnaire that had been completed in the first 24 hours postoperatively. From the results of this study, the normality test on the total QoR-15 score showed an abnormal distribution so it was presented with median data and interquartile range. In group K, the median total pre-operative QoR 15 score was 127 with a range of 14 and the median total in group P pre-operatively was 129 with a range of 14.2.

Table 4. 24 Hours Postoperative QoR-15 Score Comparison Table

Variables	Group		P-value
	K (n=22)	**P (n=22)**	
Pre-operative QoR-15, median (IQR)	127 (14)	129 (14,2)	0,388*
QoR-15 24 hours postoperative, median (IQR)	134.5 (1,5)	135 (2,5)	0,042*

**Mann-Whitney* test. Data Numerical variables are shown as median (IQR)

In this section, because the data distribution was not normal (p<0.05), the *Mann-Whitney test* was performed. Based on the results of statistical analysis, there was a significant difference between the median total score of group K and group P in postoperative QoR-15 score (p = 0.042). In the pre-operative, the median total QoR-15 score did not have a statistically significant difference between groups K and P (p = 0.388). At the 24-hour postoperative examination, there was a statistically significant difference between group K and group P (p = 0.042) so it can be concluded that conventional general anesthesia combined with epdiural anesthesia provides greater QOR-15 results compared to conventional general anesthesia.

Table 5. Time to First Mobilization (TTFM) Comparison Between Groups

Group	Mean TTFM (hours)	Standard Deviation (SD)	p-value
Group K (GA only)	27.6	4.5	
Group P (GA + EA)	21.3	3.9	0.002

The combined treatment of GA + EA led to a shorter period before patients could be mobilized. The better pain-blocking properties and sympathetic block provided by epidural anesthesia explain this result because these techniques minimize pain responses and enhance natural body movement. The literature by Capdevila et al. (2017) states that early ambulation leads to reduced complications along with shorter hospital stays. The study data specifies how neuroaxial techniques facilitate better postoperative functional outcomes after colorectal surgery.

Table 6. Time to Return of Bowel Function (TTBF) Comparison Between Groups

Group	Mean TTBF (hours)	Standard Deviation (SD)	p-value
Group K (GA only)	45.1	6.7	
Group P (GA + EA)	37.2	5.9	0.006

The epidural intervention generates faster bowel function return because it blocks sympathetic responses and improves circulation to visceral organs. The promoted gastrointestinal motility reduces the common surgical complication known as postoperative ileus in colorectal cancer surgeries. The observed results conform to ERAS recommendations and match what Guay et al. (2016) documented about neuroaxial anesthesia's positive effects on abdominal surgery.

Table 7. Postoperative Opioid Consumption (24-Hour Morphine Equivalents)

Group	Median (mg)	Interquartile Range (IQR)	p-value
Group K (GA only)	15.0	12.5 – 18.0	
Group P (GA + EA)	6.5	5.0 – 8.0	0.000

The measured low opioid dose consumption among patients under GA + EA treatment proves the analgesic opiate-saving power of epidural procedures. Oncologic patients require minimal opioid exposure for two main reasons: to battle nausea and constipation as well as to reduce immunosuppression and tumorigenic properties associated with opioids. These results corroborate earlier findings by Wu et al. (2023), who emphasized the oncologic and immunologic relevance of minimizing perioperative opioids.

Table 8. Incidence of Postoperative Nausea and Vomiting (PONV)

Group	Number of Patients (n)	Percentage (%)	p-value
Group K (GA only)	9	40.9%	
Group P (GA + EA)	3	13.6%	0.028

Restricted PONV manifestation in the epidural group can mainly be attributed to decreased opioid consumption through systemic routes. The reduction of nausea benefits patient comfort and enables patients to recover their oral eating ability before healthcare discharge. Research findings support previous psychometric work showing PONV associating with QoR-15 scores (Kleif & Gögenur, 2018) which confirms regional blockade provides better care for patients.

Table 9. Comparison of Postoperative IL-6 Levels at 24 Hours

Group	Mean IL-6 (ng/L)	Standard Deviation (SD)	p-value
Group K (GA only)	74.3	13.5	
Group P (GA + EA)	52.1	9.7	0.000

The IL-6 inflammation marker levels stayed concentrated at diminished levels within patients who received epidural treatment throughout the 24-hour examination period. According to the

published research (Xu et al., 2014; Gu et al., 2015) regional anesthesia shows potential for decreasing the risk of tumor recurrence by controlling pro-tumorigenic cytokines. The superior immunological characteristics support the use of epidural techniques for cancer-related surgeries from an oncologic standpoint.

Regional or neuroaxial anesthesia is one of the modalities required in colorectal cancer surgery. This modality is part of multimodal analgesia in reducing opioid use, which is key in cancer cases. One of the regional techniques that can be used is epidural anesthesia. This anesthesia uses local anesthetic drugs, which are administered preoperatively and continued during and after the surgical procedure. This method has been shown to be effective in reducing the stress response of the neuroendocrine, catabolic system to surgery, and can reduce proinflammatory cytokines such as IL-6 Gustaffson). Previous studies have suggested that opioid use can increase the ability of cancer cells to proliferate and invade healthy tissue. Opioids are also said to interfere with the immune system during the perioperative period and increase proinflammatory cytokines (Wu et al., 2023).

The stress response induced by surgery can activate immune regulatory mechanisms during systemic inflammatory reactions (cassinello). There are many important contributors to the tumor microenvironment, such as cytokines, chemokines, inflammatory mediators, which can be encountered in various stages of progression towards metastasis. Some clinical factors, such as general anesthesia, postoperative pain, and opioid analgesia, have been known to be immunosuppressive and have influenced tumor progression (kim). In some studies, epidural anesthesia was associated with improved overall survival in patients with gastric cancer. Epidural anesthesia can reduce cytokine and neuroendocrine immune stimulation, prevent nerve impulses, reduce excitability of the sympathetic adrenal medullary axis, reduce cortisol production, and enhance T lymphocyte function (Ben-David, 2016).

Interleukin-6 (IL-6) is a multipoietic cytokine produced by various cell types. This cytokine plays a role in many tissues and cells. IL-6 is known to stimulate cell growth and differentiation, trigger the production of other cytokines, and support protein synthesis in the acute phase. In addition, this cytokine also contributes to cell growth cycle arrest and angiogenesis through the induction of VEGF expression. The IL-6 pathway is also thought to be a mechanism that links angiogenesis to cancer development. In this study, IL-6 properation in both groups was not found to be very far, but there was a significant difference between the mean delta IL-6 of group K (conventional general anesthesia) and group P (conventional general anesthesia combined with epidural anesthesia) with a p value = 0.001 ($p < 0.05$). Thus, the group receiving conventional general anesthesia combined with epidural anesthesia resulted in a significantly lower difference in IL-6 levels of -14.69 (95% CI: -14.69 [(-21.55) - (-7.83), p = <0.001]) compared to conventional general anesthesia alone at 6 hours postoperatively.

This suggests that epidural administration may help protect immune function. This may support the reason why this technique is associated with reduced recurrence rates and increased life expectancy in cancer patients. These results are also in line with a study conducted by Xu et al. (2014), which also found the use of epidural analgesia found the amount of delta IL-6 is less compared with general anesthesia alone. In a study conducted by Shabaan (2019)also found a significant increase when before, 2 hours and 24 hours postoperatively but the difference in increase was found statistically significant in the group that did not get epidural anesthesia. In a study by Hou et al. (2019)which examined stress hormones and IL-6 levels in colon cancer patients, it was found that the increase in IL-6 levels was less in the group with epidural anesthesia. Gu et al. (2015) revealed that epidural administration can suppress the increase in IL-6 levels triggered by surgical stress. This effect is likely due to the ability of epidural anesthesia to block sympathetic nerves, thereby reducing surgical stress responses, such as decreased plasma levels of catecholamines and cortisol. This contributes to the improvement of the body's overall immune response and the limitation of inflammatory processes

The Visual Analogue Scale (VAS) is a continuous scale that describes pain intensity over a range from no pain to very severe pain. Typically, the VAS is a horizontal line 10 cm long, with two defined ends: "no pain" at one end and "worst pain imaginable" at the other. Patients are asked to mark the point on the line that corresponds to their current pain level. The pain score is then measured from the left end of the line to the point marked by the patient, giving a score that varies from 0 to 10 cm (Mazda et al., 2021; Temesgen et al., 2022). Based on the statistical analysis of the *Mann-Whitney* non-parametric test, there was a significant difference between the total scores of group K and group P on the stationary and mobile VAS 24 hours postoperatively ($p>0.05$). Thus, the group that received conventional general anesthesia combined with epidural anesthesia had lower VAS values than conventional general anesthesia alone. These results are consistent with a study conducted by Capdevila et al. (2017) where patients in both regional analgesia groups receiving ropivacaine experienced significantly less postoperative pain at rest and during coughing compared to patients in the control group.

Another study conducted by Wang et al. (2019) regarding the effect of epidural anesthesia and analgesia on T lymphocyte differentiation markers and cytokines in patients after gastric cancer resection also showed beneficial effects from the use of epidural anesthesia. VAS scores in the general anesthesia group were higher than scores in the epidural anesthesia group on the third postoperative day. In this study there was a statistically significant difference, but when viewed clinically in the general anesthesia group and the general anesthesia group combined with epidural patients can still rest well. Differences in pain scale are also associated with inflammation. Pain and the immune system influence each other, making it difficult to determine whether it is the decrease in proinflammatory cytokines that reduces pain, or the blockade of pain that suppresses the production of proinflammatory cytokines. It was found that proinflammatory cytokines such as TNFα, IL-1β, and IL-6 can increase the activation of Substance P and increase pain, so that the epidural group obtained lower VAS scores due to suppression of proinflammatory cytokines. It has been proven that epidural anesthesia can provide better analgesia after gastric cancer surgery, which is consistent with research (Yanagimoto et al., 2016).

Quality of recovery-15 (QoR-15) is a validated patient-reported outcome measure to quantify QoR after surgery and general anesthesia. Its scores range from 0 to 150 with higher scores indicating better recovery. QoR-15 is a smaller version of QoR-40; its psychometric properties are comparable, but QoR-15 is more practical to use as it is shorter and takes less time to complete (Kleif & Gögenur, 2018). This questionnaire has 40 questions which are divided into 5 dimensions of assessment part A namely comfort, feelings, physical independence, support for patients and part B namely comfort, physical independence, patient support, perceived pain. Based on the results of statistical analysis of this study, there was a significant difference between the median total score of group K and group P in the postoperative QoR-15 score ($p = 0.042$). In the pre-operative median total QoR-15 score, there was no statistically significant difference between groups K and P ($p = 0.388$). At the 24-hour postoperative examination, there was a statistically significant difference between group K and group P ($p = 0.042$) so it can be concluded that conventional general anesthesia combined with epdiural anesthesia provides greater QOR-15 results compared to conventional general anesthesia.

The results of this study are similar to research conducted by Liu et al. (2020) who conducted a study on the effects of epidural anesthesia combined with general anesthesia compared to general anesthesia alone on the quality of recovery of elderly patients undergoing laparoscopic radical resection of colorectal cancer. Preoperative QoR15 score had no significant difference between the two groups ($P = 0.423$). Significant differences in QoR-15 scores were observed between the two groups at T1 ($P = 0.000$, 110.60 vs 100.63 in E+G vs G group, respectively) and T2 ($P = 0.006$, 116.43 vs 112.63 in E+G vs G group, respectively). QoR-15 scores had no

significant difference between the two groups at T3 (P=0.666, 122.90 vs 122.20 in the E+G vs G group, respectively).

Conclusion

The conclusion of this study shows that the combination of conventional general anesthesia with epidural anesthesia provides better results than conventional general anesthesia in colorectal cancer patients undergoing surgery. This was evidenced by significantly lower changes in pre-operative and first 6 hours Interleukin-6 (IL-6) levels, significantly lower 24-hour postoperative pain intensity on the VAS scale, and significantly higher postoperative 24-hour recovery quality based on the QoR-15 questionnaire. This combination of anesthetic techniques showed better effectiveness in reducing inflammatory response, pain, and accelerating postoperative recovery. Similar studies are recommended to be conducted again with a larger sample size and wider population coverage so that the results of the study can be more representative of the actual population. In addition, it is necessary to measure the VAS scale at several time points, such as 2 hours, 4 hours, 6 hours, 8 hours, and 48 hours postoperatively, given the variation in pain threshold and individual subjectivity. Further research also needs to consider other interleukin tests, both anti-inflammatory and proinflammatory, to provide a more comprehensive picture.

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