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Original Research Article

Patients Undergoing Gastric Cancer Surgery with Epidural Combined with General Anesthesia and General Anesthesia

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Abstract: ***Background:*** Gastric cancer (GC) is one of the leading causes of mortality and morbidity and adds significantly financial burden to patient and their family on healthcare. The incidence of gastric cancer continues to increase in Bangladesh; therefore there is unmet need of promising treatment modalities. ***Objective:*** To investigate the survival of patients undergoing gastric cancer surgery with epidural combined with general anesthesia (EGA) and general anesthesia alone (GA). ***Methods:*** A retrospectively observation study was carried out at the Dept. of Anesthesia, National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh from June 2021 March 2022. 451 patients with gastric cancer who were scheduled for radical resection. Propensity score matching was performed at a 1:1 ratio between GA (n=75) and EGA (n=75) to reduce selection bias. Univariate and multivariate analyses were used to identify factors significantly correlated with recurrence and/or metastasis and prognosis. The 3-year overall survival rates of patients receiving EGA and GA alone were compared. ***Results:*** After the propensity scores were matched, there were 75 patients who underwent EGA and 75 patients who underwent GA. For the entire population, reconstruction type, pN stage, and complications were significantly correlated with prognosis based on multivariate analyses. For patients with a recurrence and/or metastasis, lymphadenectomy and pN stage were shown to be independent prognostic factors by multivariate analysis. ***Conclusions*****:** In summary, patients might benefit from EGA as a result of better analgesic and anti-inflammatory effects, fewer postoperative complications, higher safety, and a lower rate of metastasis and recurrence is conducive to postoperative recovery in patients with gastric cancer.

Keywords: Epidural Anesthesia, Gastric Cancer, Metastasis, Recurrence.

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INTRODUCTION

Gastric cancer (GC) is one of the leading causes of mortality and morbidity and adds significantly financial burden to patient and their family on healthcare [1]. The incidence of gastric cancer continues to increase in Bangladesh; therefore there is unmet need of promising treatment modalities. Of available treatment modalities for treating early stage of GC, radical surgery is the choice of surgical intervention indicated for resectable GC of early stage [2]. During the surgical intervention, surgical cuts affect the modulation of several inflammatory biomarkers such as cytokines, which causes inflammatory reactions, which greatly influence the efficacy of treatment and causes poor prognosis including overall survival [3, 4]. Thus, controlling inflammatory reactions and protecting immune function during perioperative period is essential to achieve targeted

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therapeutic response in cancer patients [5]. Previous study has shown that various perioperative elements may impair cellular immunity, thereby increasing cellular immunosuppressive effects, further inducing tumor recurrence and metastasis, and reducing the survival time of patients [6]. Therefore, protecting immune function and the stress response during the perioperative period is very important to improve the prognosis of tumor patients. Anesthesia is an inescapable application during the perioperative period, and various anesthesia methods may have different influences on postoperative recovery, short-term adverse reactions, and even tumor metastasis and recurrence [7]. One possible reason may be that anesthesia can regulate the recurrence or metastasis of cancer by directly affecting the biological behavior of tumor cells or improving the tumor microenvironment [8]. General anesthesia (GA) and epidural anesthesia are commonly used for patients undergoing gastric cancer surgery. Moreover, epidural anesthesia has the potential to reduce the incidence of side effects, cancer recurrence, and metastasis [9, 10]. Recently, the potential survival benefits of anesthesia techniques for different cancer types has received increasing attention [11]; however, the roles of anesthesia techniques in improving survival and reducing complications after cancer surgery are conflicting rather than conclusive. In a retrospective study, Christopherson *et al.* [12] concluded that the type of anesthesia did not appear to affect long-term survival after colon cancer surgery. However, another retrospective study by Zhong *et al.* [13] suggested that epidural combined with general anesthesia (EGA) can improve the prognosis of ovarian cancer after surgery. Considering the unavailability of clinical data on usage of EGA+GA and GA in population undergoing surgical intervention for gastric cancer, and controversy in the results of clinical trial for these techniques of an aesthesis.

MATERIALS AND METHODS

A retrospectively observation study was carried out at the Dept. of Anesthesia, National Institute of Cancer Research& Hospital (NICR H), Mohakhali, Dhaka, Bangladesh from June 2021 March 2022. Patients with gastric cancer without metastases who underwent gastrectomy were entered into a retrospectively maintained database. A total of 451 patients with locally advanced gastric cancer underwent total or subtotal gastrectomy. All patients achieved a potentially curative resection for histologically-proven gastric adenocarcinoma. All patient records and information were anonymized and de-identified prior to analysis. The inclusion criteria were as follows: patients with EGA or GA; complete medical records; patients <65 years of age; and lymphadenectomy. The exclusion criteria were as follows: preoperative adjuvant therapy; laparoscopic-assisted gastric cancer surgery; stage IV cancer; previous or concomitant cancer; and emergency surgery.

The patients with American Society of Anesthesiologists (ASA) score of ≥4, had history of bleeding disorder, uncontrolled diabetes, heart diseases, mental disorder, chronic renal disease, sleep disorder, pleural adhesions, and has ipsilateral thoracic surgery were excluded. Also, patients with deformity in airways or spinal, or chest wall were also excluded. The patients with any other pathology likely to affect the outcome of study, and patients who received concomitant and contra-indicated medications, as well as patients undergoing any other form of surgery, were excluded.

Treatment and study procedure: Subjects who met eligibility criteria were enrolled and received either epidural combined with general anesthesia (group EA + GA) or general anesthesia (group GA) in allocation ratio of 1:1. Intravenous fentanyl was administered to all patients as pre-anesthetic medication. The patients were monitored thoroughly the operating room and included ECG, pulse oximetry, blood pressure and respiratory rate. In EA +GA group, propofol (IV injection, 1 to 2 mg/kg), fentanyl (3 µg/kg), and rocuronium (0.6 mg/kg) were used to induce general anesthesia. Before inducing GA, an epidural catheter was inserted in L1 an L2 using the median/loss-ofresistance approach. Lidocaine (2 %) up to 3 ml as test dose was administered using epidural catheter after getting negative aspiration results of blood and cerebrospinal fluid. Then second dose of ropivacaine (0.7%) in 6 – 8 mL was administered via epidural catheter after induction of GA. Ropivacaine (0.7%, 5 mL) was administered every 1 h during surgery. All patients received sevoflurane and analgesic as a part of maintenance of anesthesia. In GA group, propofol (IV injection, 1 to 2 mg/kg), fentanyl (3 µg/kg), and rocuronium (0.6 mg/kg) were used to induce general anesthesia. Mechanical ventilator was achieved with a total volume of 8mL/kg, with positive end-expiratory pressure (PEEP) was 15 +/- 1 cm H (2)O. Ondansetron was administered as prophylaxis against nausea and vomiting. All patients received patient-controlled analgesic after end of surgery. Each patient was given opioid analgesia using PCA pump, in which morphine 100mg in 100mL of sodium chloride 0.9% (1mg per 1mL), with PCA bolus dose of 0.5mL (0.5mg) - 2.0mL (2.0 mg), the lockout time was 5 minutes. After the surgical procedure, pain score on VAS scale were measured.

STATISTICAL ANALYSIS

The present preliminary investigation designed to compare postoperative opioid consumption, inflammatory response, survival/clinical outcomes and safety profile of EA plus GA versus GA in stage 1 gastric cancer patients undergoing surgical intervention using laparoscopy. Since, the present study was designed as a pilot or preliminary investigation, thus, there is no formal calculation of sample size required. In the present preliminary investigation, we have planned to recruit at least 90 gastric cancer patients

undergoing laparoscopy in each treatment group. The finding of present study may benefit the scientific community and helps to design large clinical trial across globe. Quantitative data were analyzed using t test or Mann Whitney based on the normality of data. Categorical data were analyzed using chisquare/fisher exact test as appropriate considering the data size. KM curve was used to compare survival outcome of both the group. Cox regression model with baseline covariates. Hazard ration with p value and 95 % CI range were calculated.

RESULTS

A total of 150 patients undergoing gastric surgery were enrolled after satisfying all the eligibility criteria. All the enrolled patients have completed the study as per the study protocol. Patient characteristic is presented in Table-1. Demography and baseline characteristic were similar in both groups.

Table-1: Patient characteristics (N=150)

Variable	GA Group(n=75)	EGA Group(n=75)	P-value
Age (years)	57.2±3.1	59. 4±4.2	>0.05
Weight, kg	67.2 (3.6)	69.2 (5.6)	>0.05
BMI(kg/m2)	27.2 (1.3)	26.6±2.1	>0.05
Gender (M/F)	50/25	55/20	>0.05
ASA class (%)			
I	11	13	>0.05
II	41	40	
III	23	22	
Tumor size cm	1.4 (0.6)	1.5 (0.9)	>0.05
Anesthesia time(min)	276.23(23.1)	316.23(23.1)	>0.05
Surgical Time (time)	231.2(21.3)	236.2(21.3)	>0.05
Stage			
I	62	65	>0.05
II	10	7	>0.05
III	3	3	>0.05

Values expressed as mean (SD) for numerical variable, % of patients reported for categorical variables.

As indicated in Table 2, the patients of both the treatment group had greater reduction in postoperative pain score at each time points. However, reduction in VAS score was significantly lower in patients who received GA + EGA group as compared to patients who received GA group. At early time points, pain score after was significantly lower in patients who received epidural anesthesia combined with general anesthesia as compared to general anesthesia alone. Similar trend of results was found after 48 and 72 h of treatment (Table 2).

Table-2: Pain score assessed using VAS (N=150)

Time (h)	GA Group(n=75)	EGA Group(n=75)	P-value
3	7.2(2.2)	6.2(1.2)	<0.05
6	6.8(2.1)	5.8(1.3)	<0.05
12	5.3(2.1)	3.5(1.2)	<0.05
24	5.6(1.8)	3.2(1.3)	<0.05
48	4.6(1.2)	3.2(1.1)	<0.05
72	3.2(0.9)	1.2(0.8)	<0.05

Values expressed as mean (SD) for numerical variable. P-value is based on Unpaired t test. This was further confirmed by postoperative opioid consumption, which was significantly lower in patient who received combination of epidural and general anesthesia as compared to combination of epidural and general anesthesia from day 1 to 4 (Table 3).

Table-3: Comparing opioids consumption postoperatively (N=150)

Day	GA Group(n=75)	EGA Group(n=75)	P-value
Day 1	35(7.7)	22(4.8)	<0.05
Day 2	28(6.5)	12(2.6)	<0.05
Day 3	28(6.2)	9(1.9)	<0.05
Day 4	17(3.7)	8 (1.7)	<0.05

Values expressed as mean (SD) for numerical variable. P-value is based on unpaired t test.

Postoperative opioid consumption was significantly lower in patients who received combination of epidural and general anesthesia as compared to general anesthesia (Table 3). Moreover, number of doses of diclofenac taken post-operatively was significantly higher among patients received general anesthesia alone as compared to patients received combination of epidural and general anesthesia (Table 4). The length of hospital stay was also slightly lower in patients received combination of epidural and general anesthesia as compared to general anesthesia (Table 4). In addition, degree of pain control satisfaction was higher in patients received combination of epidural and general anesthesia as compared to general anesthesia.

Table-4: Summary of other endpoints (N=150)

Variable	GA Group(n=75)	EGA Group(n=75)	P-value
Incidence of nausea and vomiting, %	24	25.0	>0.05
Degree of pain control satisfaction	3.1(0.5)	4.2(0.4)	<0.05
Diclofenac dose (mg)	55.6(6.4)	25(4.3)	<0.05
Length of hospital stay (in days)	6(1)	5(1)	<0.05

Values expressed as mean (SD) for numerical variable. P value is based on UN paired t test. The percent viable CD3+, CD4+, CD8+ and CD4+/CD8 ratio were marginally increased in patients treated with combination anesthesia as compared to GA alone at all the timepoints (Table 5). Survival outcome in both the treatment group were comparable in both groups irrespective of type of anesthesia used during surgical intervention for gastric cancer. This indicates that use of anesthesia does not have any effect on survival outcome of gastric cancer patient. Moreover, combination of GA+EGA significantly improves the recovery time in patient undergoing laparoscopic-assisted tumor resection as compared to patients treated with GA only. Overall, incidence of nausea and vomiting was found comparable in both the groups. Postoperative results showed that the patients of both the group had comparable post-operative complications. The most common post-operative complications in patients of both the group were nausea/vomiting and CVS related complications followed by neurological related complication which was mild in severity. There was no statistically significant difference between both the groups with regard to post-operative complications.

Table-5: Summary of T lymphocyte subcategories in patients with early-stage gastric cancer (N=150)

Variable	GA group (n=75)	EGA group (n=75)	P-value
CD3+,%		54	
T1	43	43	>0.05
T2	36	36	<0. 5
T3	25	32	<0.05
T4	22	29	<0.05
T5	21		<0.05
CD4+,%			
T1	33	35	<0.05
T2	28	33	<0.05
T3	22	24	<0.05
T4	17	24	<0.05
T5	12	17	<0.05
CD8+,%			
T1	13	14	>0.05
T2	14	16	>0.05
T3	11	12	>0.05
T4	18	17	>0.05
T5	9	10	>0.05
CD4+/CD8 ratio			
T1	1.7	2.1	<0.05
T2	1.1	1.9	<0.05
T3	1.2	1.8	<0.05
T4	1.2	1.9	<0.05
T5	1.03	1.9	<0.05

Values expressed as % of patients. P-value is based on Chi-square-test

DISCUSSION

The present study results report that the level of inflammatory biomarkers such as IL-1, hs CRP, TNF-alpha, IL-8, and CEA level was significantly lesser in patients received combination of EGA and GA as compared to those patients who received only GA.

Recently, increasing evidence has suggested that the anesthesia technique may affect cancer recurrence and survival outcomes; however, no studies comparing EGA and GA on survival in patients undergoing gastric cancer surgery have been conducted. In addition, complete resection with negative margins has been recommended as the standard goal for patients with resected gastric cancer [14-16]. This indicates that response by decreasing IL-1, hs CRP, TNF-alpha, IL-8, and CEA levels. Also, treatment with GA and EGA improves the level of T lymphocyte such as CD3+, CD4+, and CD8+. The result of present study was consistent with the previous reports that combination of GA and EA inhibits inflammatory response as compared to patients received GA only, which indicates that GA + EGA improves immune response in patient undergoing surgical intervention [17,18]. It has been reported that increase level of inflammatory biomarkers such as cytokines increases immunosuppressive properties that results in tumor relapse and metastasis that substantially reduced the survival period of cancer patients. Thus, controlling inflammatory reactions and protecting immune function during perioperative period is essential to achieving targeted therapeutic response in cancer patients. The average male and female is 65 and 78 years, respectively. Therefore, the long-term effect of curative gastrectomy for gastric cancer may not be evaluable in patients >65 years of age; thus, we only included patients <65 years of age. It is worth noting that the roles of epidural anesthesia in improving survival outcomes for prostatectomies are conflicting. Biki *et al.* [19] demonstrated that patients who had GA as a substitute for epidural anesthesia for postoperative opioids following open prostatectomy surgery was associated with substantially less risk of biochemical cancer recurrence. In another retrospective study, however, no significant difference existed between GA plus postoperative ketorolac-morphine anesthesia and GA plus intraoperative and postoperative thoracic epidural anesthesia with respect to the biochemical recurrence free survival, cancer specific survival, or OS for patients undergoing open retropubic radical prostatectomies [20]. Furthermore, EGA significantly decreased the incidence of recurrence following radical prostatectomy compared with GA plus opioid infusion [21]. Similarly, the effects of epidural anesthesia on survival for patients who underwent colorectal cancer surgery are also conflicting rather than conclusive. A large cohort study conducted by Cummings *et al.* [22] confirmed that patients with non-metastatic colorectal cancer benefit from epidural anesthesia with respect to survival, rather than cancer recurrence, compared with non-epidural anesthesia. Gupta *et al.* [23] found a reduction in all-cause mortality after rectal, but not colon cancer, in patients with epidural anesthesia, as compared with patient-controlled anesthesia. EGA was confirmed to be associated with enhanced survival among patients without metastases before 1.46 years (18); however, no significant decrease in cancer recurrence was demonstrated for patients with epidural anesthesia undergoing colorectal cancer surgery compared to patients without epidural anesthesia [24]. This study results report that the patients of both treatment group had greater reduction in postoperative pain score at each time points. At early timepoints, pain score after was significantly lower in patients who received epidural anesthesia combined with general anesthesia as compared to general anesthesia alone. Similar trend of results was found after 48 and 72 h of treatment. This indicates that the combination of epidural and general anesthesia demonstrates significantly greater reduction in postoperative pain as compared to general anesthesia. This was further confirmed by postoperative opioid consumption, which was significantly lower in patient who received combination of epidural and general anesthesia as compared to combination of epidural and general anesthesia from day 1 to 4. Moreover, combination of GA + EGA significantly improves the recovery time in patient undergoing laparoscopic-assisted tumor resection as compared to patients treated with GA only. The result of present study was consistent with the previous reports that the combination of GA and EA inhibits inflammatory response as compared to patients received GA only, which indicates that EGA improves immune response in patient undergoing surgical intervention. The result of present study was consistent with the previous reports that combination of GA and EGA demonstrates significantly greater pain relief as compared to patients received GA alone, which indicates that EGA improves pain relief and improve recovery among the patient undergoing surgical intervention [17,18]. During surgical intervention, several pain management options are available such as patient-controlled analgesia (PCA), regional analgesia and regional anesthesia including epidural that are more commonly used to manage post-operative pain. Opioids analgesics as PCA such as morphine and other derivatives are most frequently used primary treatment as analgesia in patient undergoing major surgical intervention such as cancer surgery. However, the use of Opioids PCA are commonly associated with adverse events such as sedation, nausea/vomiting, and pruritus.

In this study, survival outcome in both treatment group were found comparable in both the group irrespective of type of anesthesia being used during surgical intervention of gastric cancer. The result of present study was consistent with the previous reports that combination of GA and EGA demonstrates no clinical benefit in survival outcome as compared to patients received GA alone, which indicates that GA + EGA has no role in improving survival outcome among the patient undergoing surgical intervention [25]. The use of EGA in gastric cancer surgery is increasing nowadays due to its effect on metastasis/relapse of tumor postoperatively. Also, EGA is likely to reduce the incidence of side effects and metastasis/relapse of tumor. Also, general anesthesia (GA) is commonly used gastric cancer surgical innervations. Several studies

have reported interesting findings on role of anesthetic techniques in improving prognosis of GC and reducing the post-operative complications in GC patients undergoing surgical resection of tumor. However, few studies reported that there was no relationship of anesthetic techniques and clinical prognosis of tumor. Zhong et al reported that the combination of EGA and GA (EGA plus GA) could improve the prognosis of tumor post-surgical interventions of ovarian cancer [26]. Christopherson and his coworkers showed that there are no long-term benefits of overall survival and disease-free survival outcome after surgical interventions of colon cancer using EGA and GA [27].

CONCLUSION

When compared to GA alone, the combination of EGA + GA demonstrates significantly greater reduction in post-operative pain with decreased postoperative opioid consumption. Furthermore, the combination inhibits inflammatory response, when compared to patients who received GA only, which indicates that GA+EGA improves immune response in patients undergoing surgical intervention. Moreover, combination does not demonstrate any clinical benefit in survival outcome, compared to patients who received GA alone, thus indicating that GA+EGA plays no role in improving survival outcome among patients undergoing gastric surgery.

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