

Original Research Article

Comparison of efficacy and safety of general anesthesia alone with those of combined epidural/general anesthesia in Chinese patients with gastric cancer undergoing laparoscopy-assisted tumor resection

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Abstract

Purpose: To compare postoperative opioid consumption, inflammatory response, survival/clinical outcomes and safety profile of epidural combined with general anesthesia (GA) versus GA in stage 1 gastric cancer patients undergoing surgical intervention by laparoscopy.

Method: Chinese patients with early-stage gastric cancer undergoing laparoscopic-assisted tumor resection were enrolled and received either epidural combined with general anesthesia (group EA + GA) or general anesthesia only (group GA) in allocation ratio of 1:1. The following efficacy variables were assessed: 1) Pain score was measured on VAS scale; 2) post-operative consumption; 3) Quality of recovery; 4) inflammatory response; and 5) survival outcome. Safety was assessed throughout the study period.

Results: Data for 200 subjects were analyzed. Compared to GA alone, combination of EA + GA demonstrate significantly greater reduction in post-operative pain with decrease postoperative opioid consumption. Also, the combination of GA and EA inhibited inflammatory response when compared to patients who received GA only. Moreover, the combination of GA and EA did not demonstrate any clinical benefit in survival outcome, when compared to patients who received GA alone, indicating that GA + EA has no role in improving survival outcome among patients undergoing gastric cancer surgery. Additionally, EA + GA was also associated with a shorter length of hospital stay, compared to GA.

Conclusion: Overall, the results favor the use of GA + EA in Chinese patients with early-stage gastric cancer undergoing laparoscopic-assisted tumor resection. GA + EA combination improves immune response by inhibiting the inflammatory response but has no significant effect on survival outcome.

Keywords: Inflammatory response, General anesthesia, Epidural anesthesia, Gastric cancer, Survival, Postoperative opioid consumption

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INTRODUCTION

Gastric cancer (GC) is one of the leading causes of mortality and morbidity and add significantly financial burden to patient and their family on

healthcare [1]. The incidence of gastric cancer continues to increase in China, 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 therapeutic response in cancer patients [5].

Several studies reported interesting finding on the role of anesthetic techniques in improving prognosis of GC and reducing the post-operative complications in GC patients undergoing surgical resection of tumor [6]. However, few studies reported that there was no relationship between anesthetic techniques and clinical prognosis of tumor. Zhong *et al.* reported that the combination of epidural anesthesia (EA) and general anesthesia (GA) (EA plus GA) improved the prognosis of tumor post-surgical interventions of ovarian cancer [7]. Christopherson and co-workers showed that there is no long-term benefits of overall survival and disease free survival outcome after surgical interventions of colon cancer using EA and GA [8].

In China, there is no study comparing 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 available. Considering the unavailability of clinical data on usage of EA+GA and GA in Chinese population undergoing surgical intervention for gastric cancer, and controversy in the results of clinical trial for these techniques of an aesthesis, the present study was 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.

METHODS

Patients and ethics

Chinese patients diagnosed with early-stage gastric cancer undergoing laparoscopic-assisted tumor resection were informed about the study procedures, role and responsibility of subject and investigator, then enrolled at study site after obtaining their written informed consent. The study was initiated after obtaining ethical approval from the institutional review board (IRB)

of Soochow University, *vide*, IRB approval no. IRB/SU-19-S238/R548. The study was conducted in line with the ethical principles laid down in the Helsinki Declaration and its later amendments [9]. To assess the eligibility criteria, each subject was subjected into screening visit, where blood samples for complete laboratory assessment including chest x-ray, and electrocardiogram to confirm the suitability of subject.

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 μ g/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-of-resistance 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 μ g/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.

The following efficacy variables were assessed: Pain score was measured on VAS scale (0 - 10) immediately after exiting the OT room, and at 3, 6, 12, 24, 48 and 72 h. The pain score was assessed by a blinded observer. Quality of recovery in both the group was assessed using QoL-15 tool. Also, inflammatory response and survival outcome was assessed. Also, blood sample from each patient was instantly before administration of anesthesia (T1), 2 h after starting operation (T2), instantly after surgery (T3), and thereafter after 24 h (T4), 48 (T5) and 72 hr (T5) of surgery. Inflammatory markers such as CD3+, CD4+, CD8+, CD4+/CD8+, IL-1, hs CRP, TNF-alpha, IL-8, and CEA level were measured using standard method. Also, survival outcome was measured in both groups and was assessed after discharge. Each patient was followed up for at least 3 years after discharge. Demographic and baseline characteristics as covariates to affect survival outcome were taken into consideration using cox regression model with baseline covariates. Hazard ration with p value and 95 % confidence interval (CI) range were calculated. Other key variables assessed were: AUC of VAS score, opioid consumption, length of hospital stay, treatment satisfaction as measured using degree of pain control (using 5-point Likert scale), and post-operative complications, blood loss, incidences of hypotension, and cardiopulmonary stability during surgery. Safety was assessed throughout the study period.

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 100 Chinese 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 chi-square/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 200 Chinese patients undergoing gastric surgery were enrolled after satisfying all the eligibility criteria. All the enrolled Chinese 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

Variable	GA Group (N=100)	GA + EA Group (N=100)	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/m ²)	27.2 (1.3)	26.6±2.1	>0.05
Gender (M/F)	75/35	70/40	>0.05
ASA class (%)			
I	21	23	>0.05
II	49	46	
III	30	31	
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	87	87	>0.05
II	10	10	>0.05
IIa	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 post-operative pain score at each time points. However, reduction in VAS score was significantly greater in patients who received GA + EA 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

Time (h)	GA Group (N=100)	GA + EA Group (N=100)	P-value
3	7.2 (2.2)	6.2 (1.2)	<0.005
6	6.8 (2.1)	5.8 (1.3)	<0.005
12	5.3 (2.1)	3.5 (1.2)	<0.005
24	5.6 (1.8)	3.2 (1.3)	<0.005
48	4.6 (1.2)	3.2 (1.1)	<0.005
72	3.2 (0.9)	1.2 (0.8)	<0.005

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 post-operatively

Day	GA Group (N=100)	GA + EA Group (N=100)	P-value
Day 1	45 (3.5)	23 (1.1)	<0.005
Day 2	38 (6.5)	14 (1.1)	<0.005
Day 3	34 (7.5)	9 (1.4)	<0.005
Day 4	27 (4.8)	8.5 (1.5)	<0.005

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

Postoperative opioid consumption was significantly higher 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 longer 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

Variable	GA group(N=100)	GA + EA group (N=100)	P-value
Incidence of nausea and vomiting, %	24.4	25	>0.05
Degree of pain control satisfaction	3.1 (0.5)	4.2 (0.4)	<0.005
Diclofenac dose (mg)	55.6 (6.4)	25 (4.3)	<0.005
Length of hospital stay (in days)	6 (1)	5 (1)	<0.005

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).

Overall, 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 EA and GA as compared to those patients who received only GA (Figure 2).

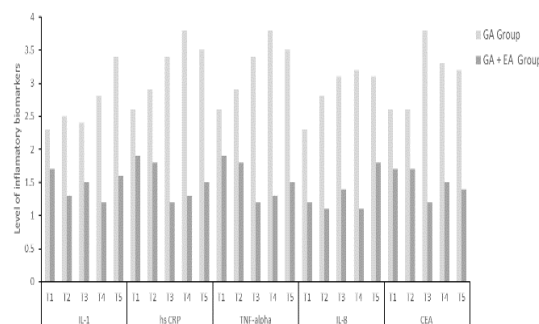


Figure 2: Summary of inflammatory biomarkers in patient Chinese patients with early-stage gastric cancer undergoing laparoscopic-assisted tumor resection

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 + EA 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. Post-operative 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 were 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 patient Chinese patients with early-stage gastric cancer undergoing laparoscopic-assisted tumor resection

Variable	GA group (N=100)	GA + EA group (N=100)	P-value
CD3+, %			
T1	53	54	>0.05
T2	46	53	<0.5
T3	35	48	<0.05
T4	32	42	<0.05
T5	31	39	<0.05
CD4+, %			
T1	43	45	<0.05
T2	38	43	<0.05
T3	32	34	<0.05
T4	27	34	<0.05
T5	22	27	<0.05
CD8+, %			
T1	23	24	>0.05
T2	24	26	>0.05
T3	21	19	>0.05
T4	28	27	>0.05
T5	15	14	>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 EA and GA as compared to those patients who received only GA. This indicates that response by decreasing IL-1, hs CRP, TNF-alpha, IL-8, and CEA levels. Also, treatment with GA and EA 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 + EA improves immune response in patient undergoing surgical intervention [10-14]. 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.

This study results report that the patients of both treatment group had greater reduction in post-operative 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 + EA 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 GA+EA improves immune response in patient undergoing surgical intervention. The result of present study was consistent with the previous reports that combination of GA and EA demonstrates significantly greater pain relief as compared to patients received GA alone, which indicates that GA+EA improves pain relief and improve recovery among the patient undergoing surgical intervention [10-14].

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 EA demonstrates no clinical benefit in survival outcome as compared to patients received GA

alone, which indicates that GA + EA has no role in improving survival outcome among the patient undergoing surgical intervention [10]. The use of EA in gastric cancer surgery is increasing nowadays due to its effect on metastasis/relapse of tumor postoperatively. Also, EA 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.

The choice of anesthesia is vital in surgical intervention while performing surgical resection of tumor as it affects recovery, side effects and metastasis/relapse of tumor. 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 EA and GA (EA plus GA) could improve the prognosis of tumor post-surgical interventions of ovarian cancer [7]. Christopherson and his co-workers showed that there are no long-term benefits of overall survival and disease-free survival outcome after surgical interventions of colon cancer using EA and GA [8]. The present study reports are consistent with the finding of Christopherson and his co-workers [8].

Limitations of the findings

Since the present trial was conducted at a single hospital in China, the findings of the present trial cannot be generalized to the Chinese population. Due to lower sample size, the power of trial was less; hence, a large clinical trial with appropriate sample size is needed to confirm the present findings.

CONCLUSION

When compared to GA alone, the combination of EA + 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+EA 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+EA plays no role in improving survival outcome among patients undergoing gastric surgery.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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