

Original Research Article

Comparison of efficacy and safety profiles of epidural analgesia and opioid analgesia in Chinese patients with thoracic trauma: A preliminary report

Xiaoping Yang¹, Danjie Zhang¹, Deling Kong², Jin Zhang¹, Bingwen Dang^{3*}

¹Department of Thoracic Surgery, ²Department of Nursing, The Second Affiliated Hospital of Xi'an Jiaotong University (Xibei Hospital), Xi'an, Shaanxi 710009, ³Department of Anesthesiology, Yulin No. 2 Hospital, Yulin, Shaanxi 719000, China

*For correspondence: **Email:** 43056862@qq.com; **Tel:** 0086-0912-3362001

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Abstract

Purpose: To compare the efficacy and safety profiles of epidural analgesia (EA) and opioid analgesia (OA) in Chinese patients with thoracic trauma (TT).

Methods: Patients with confirmed diagnosis of thoracic trauma were given either EA (via a catheter) or slow-release OA. The following efficacy variables were assessed in the two treatment groups: pain score, and changes in cytokine and catecholamine levels from baseline after treatment. Moreover, respiratory parameters were determined before and after treatment. The safety associated with each anesthesia was also evaluated. Quantitative data were analyzed either with Student's t-test or Mann-Whitney test, while categorical data were analyzed using Fisher exact or Chi-square test, based on data size.

Results: A total of 200 patients completed the study (100 patients in each group). Pain, as assessed by verbal rating scale (VRS), was slightly lower in patients after treatment with EA, when compared to the patients treated with OA. However, the difference was not statistically significant ($p < 0.05$). Maximum inspiratory force (cmH₂O) and tidal volume (liters) were slightly improved in patients treated with EA, when compared to OA-treated patients, although the difference was not statistically significant ($p < 0.05$). Moreover, the two treatments produced comparable levels of cytokines and catecholamines.

Conclusion: The efficacy and safety data for EA and OA in Chinese non-obese patients with TT indicate numerically favorable outcome for EA, when compared to OA.

Keywords: Epidural analgesia, Opioid analgesia, Chinese patients, Thoracic trauma

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INTRODUCTION

Thoracic trauma (TT) is one of the foremost causes of death worldwide. It ranks 2nd after head injury as the most frequent cause of death in USA [1-3]. In TT, impairment of respiratory function may lead to hypoxemia, proliferation in

shunt segment and pneumonia, which may require mechanical ventilation [4-8]. Moreover, there is need for adequate therapeutic aid to the thoracic region to ensure intense inhalation so as to clear discharges efficiently and prevent respiratory difficulties. Earlier reports have revealed that epidural analgesia offers

advantages over intrapleural route of administration of analgesic agents, and further improves respiratory function in TT patients [5-10]. Any kind of damage produces a variety of physiologic reactions. The neuroendocrine structure reacts through augmented action which comprises sympathetic and parasympathetic activities, including cardiac tissue-related impairment [11-14]. Sensory pain is produced by activation of nociceptor via inducements. The impulses travel through afferent nerves and reach the brain via the spinal cord where they release substance P in CNS. Then, the pain impulses travel from CNS to the injured site via the spinal cord, causing activation of sympathetic nerve-facilitated vasoconstriction and discharge of CRF (corticotrophin-releasing factor). It has been reported that patients undergoing thoracotomy had decreased levels of catecholamine [7-9].

Cytokines such as TNF (tumor necrosis factor- α), and interleukin (IL) -1, IL-2, IL-6 and IL-8 are released immediately after tissue/cell damage. The levels of TNF increase immediately after injury, whereas IL-2 levels decrease after injury. Moreover, the levels of IL-1, IL-6 and IL-8 are increased immediately after injury, and they remain elevated for a few days [6-11].

Several reports have shown the potential benefit of using epidural analgesia (EA) in TT, relative to palliative care, thereby promoting the use of EA in TT. However, the clinical use of EA has been restricted due to unfavorable risk-benefit ratio. The most common safety concern associated with EA is site reactions. Apart from site reactions, lack of efficacy is the second most common safety concern reported in several publications [10-15].

The efficacy and safety profiles of EA have not yet been compared with those of the opioid analgesia (OA) in Chinese TT patients. Thus, the present preliminary investigation was designed to compare the efficacy and safety profiles of EA and OA in Chinese patients with TT.

METHODS

Patients and ethics

Chinese TT patients having at least 3 rib side fractures with segmented flap chest and respiratory bruise, who met all eligibility criteria had the study procedures explained to them, as well as the roles and responsibilities of the patients and investigator. Then, they were

enrolled at Yulin No. 2 Hospital, China after obtaining their written informed consent. All study-related documents including protocols, ICFs and CRFs were approved. The study was initiated after prior ethical approvals from the institutional ethic committee of Yulin Hospital (*vide* approval no. IEC-YH-SX-2019/04-Y). The study was carried out in line with the ethical principles laid down in the Declaration of Helsinki and its later amendments [16]. Subjects with infection or sepsis or sign of SCI injury, and other contraindications at catheter site for EA were excluded. Moreover, obese patients with adrenal deficiency who were concomitantly on steroids in the previous six months, were excluded. Patients requiring vasoconstriction agents for control of blood pressure, HIV patients, pregnant patients, and those incapable of talking efficiently, as well as patients with history of aversion for LA and/or opioids, were excluded. In addition, subjects with severe lung diseases, lung cancer or any other type of lung cancer, were excluded.

Treatment procedures and assay protocols

Subjects who met eligibility criteria were randomly assigned to epidural analgesia (EA) or opioid analgesia (OA) group, with allocation ratio of 1:1. Fentanyl, an opioid antagonist, was administered in both groups as pre-anesthetic agent. Epidural analgesia was administered through an epidural catheter, whereas opioid analgesia (iv morphine, 1mg/kg) was administered using patient-controlled analgesia technique.

All subjects who were in OA groups were instructed and trained on dose administration system of morphine. Epidural analgesia contained lidocaine and ephedrine as pain-relieving agents. Ephedrine was added to lidocaine since it increases the duration of anesthetic action, leading to longer duration of pain relief. In both groups, blood samples were collected for assay of cytokine levels. The blood samples were centrifuged immediately at 2000 rpm and kept below 80 °C before the start of cytokine estimation.

Moreover, the levels of catecholamines (noradrenaline and adrenaline) were measured before and after treatment.

Efficacy and safety assessment

Data on demography and baseline characteristics were collected for the two study groups. The following variable indices were

determined in the two treatment groups: pain score as index pain relief, changes in cytokine levels from baseline after treatment, and changes in catecholamine levels from baseline after treatment. Moreover, respiratory parameters were measured before and after treatment. The safety of each study drug was assessed by taking note of the number of patients who experienced adverse events, including site reactions. The treatment efficacy variables such as pain relief, cytokine levels, catecholamine levels and respiratory parameters were determined at days 1, 2 and 3. Thereafter, comparison was made between EA and OA with respect to efficacy and safety parameters.

Statistical analysis

The present pilot/preliminary investigation was designed to evaluate and compare efficacy and safety profiles of EA and OA in Chinese non-obese TT patients. Hence, there was no formal calculation of sample size. A total of 100 Chinese TT patients were enrolled in each treatment group. Numerical data showing bell-shaped curve were analyzed using unpaired *t*-test, while numerical category data that did not produce bell shaped curve were analyzed using Mann-Whitney test after normality assessment. Quantitative data are presented as mean \pm SD, while categorical data are presented as percentage/proportion of patients, and were analyzed using Fisher exact test or chi-square test, based on data size.

RESULTS

A total of 200 patients completed the study (100 patients in each group). Data on demography and baseline characteristics were similar in both treatment groups (Table 1).

Pain score after treatment with EA and OA in Chinese non-obese TT patients is presented in Figure 1. Using VRS, pain after treatment with EA was slightly less, when compared to pain in patients who were treated with OA. However, the difference was not statistically significant. At baseline, there was no significant difference in pain score. On day 1, patients treated with EA experienced slightly less pain sensation than patients treated with OA, although the difference was not statistically significant. Similar trends in results were observed for day 2 and day 3. Overall, treatment with EA offered slightly better relief of pain associated with TT than treatment with OA.

Figure 1: Pain score after treatment with EA and OP in Chinese non-obese TT patients

Maximal Inspiratory force (cmH₂O) values after treatment of Chinese non-obese TT patients with EA and OA are presented in Figure 2. Max Inspiratory force (cmH₂O) after treatment with EA was slightly improved, when compared to the corresponding value for patients who were treated with OA. However, again, the difference was not statistically significant. At baseline, there was no significant difference in inspiratory force.

Table 1: Characteristics of Chinese non-obese TT patients

Outcome variable	EA group (n=100)	OA group (n=100)
Age (years)	42.5 (2.1)	41.2 (3.1)
BMI (kg/m ²)	24.1 (1.1)	23.6 (2.4)
Gender (M/F)	70/30	75/25
Severity score (injury score)	25.7 (2.1)	26.8(1.1)
Severity score (Thoracic injury abridged score)	3.6 (1.5)	3.4 (1.2)
Duration of hospital stay	8.3 (1.9)	10.6 (1.3)
Duration of stay (days) ICU	3.1(1.1)	4.2 (1.8)
Duration of stay (days) ward	5.4 (1.3)	6.2 (2.1)

Values are as mean \pm SD for all variables except gender. For each parameter, *p* > 0.05 vs IA group using appropriate statistical test

On day 1, patients treated with EA experienced slightly better maximal inspiratory force than patients who were treated with OA. However, the difference was not statistically significant. A similar trend in results was observed for day 2 and day 3. On day 3, improvement in maximal inspiratory force was significantly greater in patients treated with EA than in patients treated with OA. Overall, treatment with EA offered slightly better maximal inspiratory force than treatment with OA.

same pattern of results was obtained on the other days (day 1, day 2 and day 3) after treatment. On day 3, improvement in TV was significantly greater in patients treated with EA than in those treated with OA. Overall, EA treatment resulted in slightly better TV than treatment with OA.

Figure 2: Maximum inspiratory force (cmH₂O) after treatment with EA and OP in Chinese non-obese TT patients

The effects of EA and OA treatments on tidal volume (TV) (liters) in Chinese non-obese TT patients are presented in Figure 3. Tidal volume (liters) after treatment with EA was slightly improved, when compared the corresponding tidal volume associated with OA treatment. However, the difference was not statistically significant. At baseline, there was no significant difference in inspiratory force. However, on day 1, patients treated with EA had slightly better TV than those who were treated with OA. However, the difference was not statistically significant. On day 2, patients treated with EA experienced slightly better TV than those who were treated with OA, although the difference was not statistically significant. On day 3, patients treated with EA had slightly better TV than patients who were treated with OA, although the difference was not statistically significant. The

Figure 3: Tidal volume after treatment with EA and OA in Chinese non-obese TT patients

The effects of EA and OA on cytokine levels of Chinese non-obese TT patients are shown in Table 4. Levels of IL-1, IL-1b and IL-2 and TNF- α were decreased in the two treatment groups at day 1, day 2 and day 3 after treatment. From day 1 to day 3, levels of the cytokines were similar in both groups, whereas IL-6 level was higher at day 1, 2 and 3 in both treatment groups.

The level of IL-6 was slightly lower in patients treated with EA than in those treated with OA. However, the difference was not statistically significant. In addition, IL-8 levels were significantly lowered in both treatment groups, when compared to baseline levels. There was higher reduction in IL-8 from baseline in patients treated with EA than in those treated with OA, and the reduction in EA group was statistically greater than that in OA group. Low levels of IL-8 are helpful in reducing infection and inflammatory reaction at trauma sites.

Table 4: Cytokines levels after treatment with EA and OP in Chinese non-obese TT patients

Outcome variable (pg/mL)	EA group (n=100)	OA group (n=100)
TNF- α	8.5 \pm 2.4	9.6 \pm 2.1
IL-1	4.4 \pm 2.3	5.6 \pm 2.8
IL-1b	12.2 \pm 4.6	14.3 \pm 4.3
IL-2	16.7 \pm 5.3	17.3 \pm 4.7
IL-6	119.2 \pm 12.6	117.3 \pm 14.3
IL-8	9.2 \pm 2.1	11.3 \pm 3.3

Values are presented as mean \pm SD for all variables except gender. $P > 0.05$, vs OA group for all comparisons for each parameter using appropriate statistical test

Table 5: Catecholamine levels after treatment with EA and OP in Chinese non-obese TT patients

Outcome variable (pg/mL)	EA group (n=100)	OA group (n=100)
Blood levels of catecholamines (ug/L)		
Adrenaline	24.7±6.8	25.6±7.8
Nor-adrenaline	174.4±12.8	179.2±17.3
Urine levels of catecholamines (ug/L)		
Adrenaline	22.2±4.8	24.3±5.6
Nor-adrenaline	185.7±15.8	187.8±19.4

Values are presented as mean ± SD for all variables except gender. $P > 0.05$ vs OA group for all comparisons for each parameter using appropriate statistical test

These results indicate that EA produced slightly better and favorable outcome through regulation of cytokine levels, when compared to OA. However, there was no statistically significant difference between the two treatment groups in terms of cytokine levels.

The effects of EA and OA on catecholamine levels in urine and blood of Chinese non-obese TT patients are shown in Table 5. Catecholamine levels (epinephrine and norepinephrine) were decreased in both treatment groups at days 1, day 2 and day 3 after treatment, when compared to baseline values. From day 1 to day 3, levels of catecholamine in plasma and urine in both treatment groups were similar i.e., there were no statistically significant differences between the two treatment groups.

The levels of epinephrine and norepinephrine were slightly lower in patients treated with EA than in those given OA. The reductions in epinephrine and norepinephrine from baseline were more in patients treated with EA than in those given OA, and the reduction in EA group was statistically greater than the reduction in OA group. Overall, treatment with EA produced slightly better and more favorable outcome via regulation of epinephrine and norepinephrine levels than treatment with OA. However, there was no statistically significant difference between the two treatment groups in terms of catecholamine levels.

DISCUSSION

The present study is the first preliminary investigation that evaluated the efficacy and safety profiles of EA and OA in Chinese non-obese patients with TT. Opioid analgesia is one of standard interventions for the management of TT. Earlier reports have revealed that epidural analgesia offers advantages over intrapleural route of administration of analgesic agents, through improvement of respiratory function in TT patients. However, the benefits of

epidural analgesia in Chinese patients with TT were not established before now. Moreover, the effect of epidural analgesia on biomarkers such as cytokines (TNF, IL-1, IL-2, IL-6 and IL-8) and catecholamines (adrenaline and nor-adrenaline) were not evaluated. In the present study, the effects of EA and OA on biomarkers involved in inflammatory reaction of TT were compared. The results showed that pain after treatment with EA was slightly reduced when compared to pain in patients who were treated with OA. However, the difference was not statistically significant. At baseline, there was no significant difference in pain score. A similar trend in results was observed for day 2 and day 3.

In all, treatment with EA offered slightly better relief of pain associated with TT than treatment with OA. Thoracic injury abridged score and other scores were comparable between both groups at baseline. In addition, there was no significant difference in inspiratory force at baseline. Maximal inspiratory force after treatment with EA was slightly improved, relative to the corresponding value in patients who were treated with OA. However, the difference was not statistically significant. Overall, treatment with EA offered slightly better maximal inspiratory force than treatment with OA. Tidal volume (liters) after treatment with EA was slightly improved, when compared to treatment with OA, but the difference was not statistically significant. At baseline, there was no significant difference in inspiratory force.

Overall, treatment with EA resulted in slightly better tidal volume than treatment with OA. The level of IL-6 was slightly lower in patients treated with EA than in those treated with OA. However, the difference was not statistically significant. In addition, the level of IL-8 was significantly lower after treatment in both groups, when compared to baseline. Reduction in IL-8 from baseline was more in patients treated with EA than in those treated with OA, and the reduction in EA group was statistically greater than that in OA group. Low levels of IL-

8 are beneficial in reducing infection and inflammatory reaction at trauma sites.

Overall, EA produced slightly better and favorable outcome via regulation of cytokine levels, when compared to OA, although there were no statistically significant differences between both treatment groups in terms of cytokine levels. Moreover, catecholamine levels in plasma and urine in both groups were comparable. The observed efficacy of EA is similar to results from previous published studies which showed positive effect of EA on TT [8-15]. The efficacy of EA in TT was supported by decreased levels of cytokines and catecholamines. Moreover, the efficacy in terms of decrease in pain score was comparable with gold standard therapy. Based on the efficacy results, the use of EA may be recommended for Chinese patients with TT.

Comparison of safety outcome parameters such as incidence of complications/adverse events between both groups revealed that they were comparable. In the two groups, there were changes in vital signs, but there were no abnormalities in either group. The finding in the present study with respect to OA is consistent with results of previous studies, irrespective of type of injury or trauma. Intravenous analgesia is costly and may aggravate substantial postoperative pain. It is very evident that the choice of appropriate analgesic agent with anti-inflammatory properties has a significant influence on TT.

Overall, efficacy and safety evaluation of EA and OA in Chinese non-obese patients with TT showed numerically favorable outcome for EA, when compared to OA. This finding may be of benefit to scientific community in the design of large clinical trials for evaluating the efficacy and safety profiles of EA and OA in Chinese non-obese patients with TT across the globe.

Limitations of the study

Since the present preliminary trial was conducted in a single hospital in China, the findings cannot to be generalized to the Chinese population. However, the results should form a basis for conducting large multi-centric clinical trials with large sample sizes for verification and confirmation of the findings.

CONCLUSION

Comparison of the efficacy and safety of EA and OA in Chinese non-obese patients with TT indicate a numerically favorable outcome for EA.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We 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 the authors. Xiaoping Yang, Danjie Zhang, Deling Kong, Jin Zhang carried out the literature survey, and Bingwen Dang analysed and compiled the data. All the authors read the paper thoroughly and approved it for publication.

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