Assessing the analgesic efficacy of oral epigallocatechin-3-gallate on epidural catheter analgesia in patients after surgical stabilisation of multiple rib fractures: a prospective double-blind, placebo-controlled clinical trial

Lihong Zhang, Weifeng Liu, Haiping You, Zhiyuan Chen, Liming Xu and Hefan He

Department of Anesthesiology, Second Affiliated Hospital, Fujian Medical University, Quanzhou, China

ABSTRACT

Context: Thoracic trauma results in multiple rib fractures (MRF), and surgical stabilisation of rib fractures (SSRF) can relieve fracture pain. Epigallocatechin-3-gallate (EGCG) is reported to exhibit beneficial effects in bone-related metabolic and differentiation processes.

Objective: To study the clinical effect of EGCG on regional analgesia for pain relief in MRF patients after SSRF.

Materials and methods: Ninety-seven MRF patients (61 males, 36 females) who were on epidural catheter analgesia after SSRF were recruited. They were randomly divided into: oral EGCG 100 mg (oral grade) twice daily for 10 days and placebo groups. Pain scores, incentive spirometry (IS) volumes, respiratory rate and oxygen saturation (SpO2) were assessed day 10 after SSRF.

Results: Comparing results from the placebo and EGCG group, in the 10-day intervention course, oral EGCG reduced pain score (8 at base line vs. 4 at end of intervention in EGCG group, \( p < 0.05 \); 4 in EGCG group vs. 6 in placebo group at end of intervention, \( p < 0.05 \)), improved IS volume (713 at base line vs. 1072 at end of intervention in EGCG group, \( p < 0.05 \); 1072 in EGCG group vs. 953 in placebo group at end of intervention, \( p < 0.05 \)) and respiratory rate (24 at base line vs. 15 at end of intervention in EGCG group, \( p < 0.05 \); 15 in EGCG group vs. 19 in placebo group at end of intervention, \( p < 0.05 \)). However, no further enhancing effect on SpO2 was observed in the EGCG group (0.98 in EGCG group vs. 0.98 in placebo group at end of intervention, \( p > 0.05 \)).

Discussion and conclusions: Although the study is limited by a relatively small sample size and lack of serum factor analysis, the key results and the study design, for the first time, nevertheless pave the way for trials with larger number of patients to understand the effect of EGCG in MRF patients that are undergoing SSRF.

Introduction

Thoracic trauma frequently results in multiple rib fractures (MRF), which occur in over 60% of all thoracic trauma incidences (Simon et al. 2005). Based on statistical reports, 300,000 patients suffered from rib fractures in 2004 in the USA alone (Lafferty et al. 2011), and increased to over 350,000 cases in 2017 (Pieracci et al. 2017). Surgical stabilisation of rib fractures (SSRF) can prevent rib shortening and displacement, relieve fracture pain, and reduce the risk of non-union. Importantly, SSRF can improve ventilation, reduce dependence on ventilators and the incidences of complications such as pneumonia, length of hospital stay, and rates of mortality and disability (Solberg et al. 2009; Fraser et al. 2017). MRF are commonly seen in injuries caused by high energy mechanisms (Haenel et al. 1995). Pain, as a result of MRF, is mainly associated with decreased respiratory effort, leading to failure to clear secretions, atelectasis, and reduced vital capacity. Necessary pain management for MRF not only provides relief of symptoms, but also prevents secondary respiratory complications and decreases splinting (Fusco et al. 2017).

In MRF patients, local/regional analgesic techniques, compared to systemic analgesia, have been demonstrated to yield greater efficacy and fewer side effects (Karmakar & Ho 2003; Ho et al. 2011). Epidural (EPI) catheter analgesia is currently the most frequently studied regional technique (Lynch et al. 2019), and is recommended by the Eastern Association for the Surgery of Trauma and Trauma Anaesthesiology Society (Galvagno et al. 2016). However, the studies associated with EPI analgesia have been controversial (Lynch et al. 2019), thus warranting additional investigations to identify novel agents for further pain relief, especially in MRF patients after SSRF.

Green tea is a non-fermented and non-oxidized product containing several polyphenolic catechins, with epigallocatechin-3-gallate (EGCG) as one of the most biologically potent components (Liao et al. 2001). Various reports have suggested the beneficial effects of EGCG in bone-related metabolic and differentiation processes (Shen et al. 2009). For instance, EGCG could promote healing of femoral bone defects (Lin et al. 2019). Oxidative EGCG coating on polymeric substrates has been demonstrated to regulate activities of multiple cell types that are beneficial for healing of bone fractures (Madhurakkat...
Perikamana et al. 2019). However, the role of EGCG in pain management of MRF has yet to be investigated.

In the current clinical study, we recruited MRF patients, who were on EPI catheter analgesia after SSRF, and administered oral EGCG, followed by assessing their pain scores, incentive spirometry (IS) volumes, respiratory rates, and oxygen saturation (SpO₂). The objective of the study was to assess the analgesic efficacy of oral EGCG in MRF patients who were on EPI catheter analgesia after SSRF.

Patients and methods

Patients

All patients were recruited from those admitted into the Emergency Department of Second Affiliated Hospital, Fujian Medical University for MRF. This clinical trial was approved by the Ethics Review Board of Second Affiliated Hospital, Fujian Medical University, and registered with Chinese Clinical Trial Registry (Clinical Trial Registration Number ChiCTR 1900028247). All recruited patients have given written informed consent forms, and their data were completely de-identified to keep their confidentiality.

The study population consisted of 97 MRF patients who underwent complete evaluation including chest 3D-computed tomography and met the inclusion and exclusion criteria for undergoing SSRF in Second Affiliated Hospital, Fujian Medical University from January 2017 to December 2018.

Inclusion criteria were: 1) at least 18 years old; 2) MRF (4 or more fractured ribs) with bictorical displacement; 4) intractable pain with visual analogue scale ≥ 6 after conservative treatment (Nirula et al. 2009).

Exclusion criteria were: 1) serious head trauma with a Glasgow coma scale < 14; 2) multiple trauma at body regions outside the chest with an abbreviated injury scale score ≥ 3; 3) massive hemothorax or injury to the trachea or bronchus that required emergent surgery; 4) mechanically ventilated; 5) dementia; 6) coagulopathy.

SSRF technique

Our standard SSRF procedure combined video-assisted thoracoscopic surgery (VATS) and open reduction internal fixation (ORIF), using a muscle-sparing approach without thoracotomy (Ali-Osman et al. 2018). Moreover, to prevent iatrogenic injury (ORIF), using a muscle-sparing approach without thoracoscopic surgery (VATS) and open reduction internal fixation

Our standard SSRF procedure combined video-assisted thoracoscopic surgery (VATS) and open reduction internal fixation (ORIF), using a muscle-sparing approach without thoracotomy (Ali-Osman et al. 2018). Moreover, to prevent iatrogenic injury (ORIF), using a muscle-sparing approach without thoracoscopic surgery (VATS) and open reduction internal fixation (Chou SS et al. 2011). After SSRF, the MRF patients were admitted into the Intensive Care Unit (ICU) with endotracheal tubes in place.

EGCG (N=49)  Placebo (N=48)

Figure 1. Flow chart of the study.

EPI analgesia

In general, patients who required EPI had a pharmacologic thromboprophylaxis (PTP) hold for 12 h before the procedure as a safe window, followed by PTP provided as 40 mg enoxaparin sodium once per day. EPI was administered as continuous infusion using a fixed electronic infusion device with portless tubing, with patients in a 25° head of bed elevation. EPI analgesia was achieved as a combination of 0.1% bupivacaine with 5 μg/mL fentanyl at 4 mL/h rate for approximately 3 h per day during the course of the study. IS was encouraged ten times per h while patients were awake.

Group assignment and intervention

The 97 patients were divided using a permutated randomisation method stratified according to their baseline pain scores, with 49 in the EGCG group and 48 in the placebo group. In the EGCG group, patients were administered one capsule containing 100 mg EGCG (oral grade, purity > 94%; purchased from Taiyo International, Yamadacho, Japan), twice daily. In the placebo group, patients were administered one capsule containing 100 mg glucose (instead of EGCG), twice daily. Both types of capsules were identical in appearance to mask their contents to both the investigators and patients. Both interventions last for 10 days.

Endpoints

Primary endpoint was pain score measured using a standard 0-10 numeric rating scale (NRS), with 0 indicating no pain at all and 10 indicating the worst possible pain. Secondary endpoints included IS volume, respiratory rate, and SpO₂. All assessments were performed at the hospital admission (day 0, baseline) and at the end of intervention (day 10) by bedside nurses who were blind to the group assignment.

Statistical analysis

Statistical analysis was performed using the Graphpad software version 7. Data in the current study were found to be non-normally distributed therefore shown as median and interquartile range. P-value was calculated as two-sided and p < 0.05 was considered to indicate statistically significant difference between groups.

Results

From January 2017 to December 2018, 97 patients with MRF who underwent SSRF and received EPI analgesia met the inclusion and exclusion criteria. As shown in Figure 1, they were divided into two study groups, with 49 patients in the EGCG group and 48 in the placebo group. Demographic data of patients in
Multiple previous studies have implicated EGCG in various animal models of pain management. In murine models of chronic neuropathic pain, EGCG was shown to significantly improve pain behaviours, likely mediated by inhibiting Toll-like receptor 4 (Kuang et al. 2012) and blocking expression of nitric oxide synthase (Choi et al. 2012). Moreover, EGCG could also inhibit radiculopathic pain in rats (Krupkova et al. 2014). In a mouse model of bone cancer pain, EGCG exhibited anti-nociceptive functions in the pain progression following metastasis of bone tumour (Li & Zhang 2015). In clinical settings, an ointment containing EGCG as the active component was able to promote wound healing and relieve episiotomy pain in primiparous women (Shahrahmani et al. 2018). In addition, in patients with shoulder pain, EGCG treatment was reported with a potential to relieve rotator cuff tendinopathy-related pain and symptoms (Feng et al. 2019).

Our current study is the first instance to provide experimental evidence, in a clinical setting, that supports an adjuvant beneficial role of EGCG to enhance the effect of EPI analgesia in the pain management after SSRF for MRF patients. In general, EPI analgesia greatly relieved pain scores, which was the primary endpoint, in MRF patients after their SSRF operation. Additional oral administration of EGCG in the 10-day intervention course further reduced pain scores compared to the placebo treatment. As the secondary endpoints, IS volume and respiratory rate were also further improved by EGCG, when combined with EPI analgesia. Although such EGCG-related improvements were absent in terms of SpO2, the outcomes in IS volume and respiratory rate implied that EGCG could also improve recovery of MRF patients in functional aspects after SSRF. Sufficient analgesia is reported to improve respiratory mechanics, enhance functional capacity and prevent pulmonary complications (Brown & Walters 2012; Brasel et al. 2017; Fusco et al. 2017). In line with this notion, our results are more clinically relevant, as the primary outcome of pain score was correlated with improved pulmonary functions, thereby demonstrating a promising potential for EGCG to exert additional clinical benefits on top of conventional EPI pain management.

Rib fractures often result from blunt chest trauma and are the main cause of hospital admission. Rib fractures result in pain and disability, and many patients also develop pneumonia and/or chest wall deformity. Previous randomised controlled trials have shown that, SSRF is superior to conservative treatments for patients with flail chest and respiratory failure (Granetzny et al. 2005). Review articles and meta-analyses also showed that SSRF could reduce ICU and hospital length of stay, duration of ventilation, and tracheostomy rate. The indications for SSRF have been well established based on expert consensus.

However, poor pain control means that patients’ active mobilisation is impeded by persistent pain, despite optimised medical treatment with morphine mimetics and non-steroid anti-inflammatory drugs. Locoregional pain relief with para-vertebral blockade or EPI analgesia is ambiguous in the sense that, it cannot be used over a prolonged period, but rib fractures are still unstable and painful at 4-6 days after the initial trauma (Olland et al.
Our 10-day EGCG oral administration, although still considered a short-term intervention, may serve as a less invasive but prolonged adjuvant analgesia option beyond the limitation of EPI analgesia.

Nevertheless, there are several limitations in our current investigation. 1) It was a single centred study; therefore, our prospective results should be verified in a multi-centred study for generality considerations. 2) The sample size was relatively small; therefore, a larger sample pool would definitely bring more sophisticated statistical analysis and facilitate the identification of associated risk factors. 3) No serum factors known to be regulated by EGCG were assessed in the current study; future investigations are needed to identify the potential molecular mechanism underlying the observed benefits of EGCG in this setting.

Conclusions

In this double-blind, placebo-controlled trial, we have demonstrated that oral EGCG administration could enhance pain management of EPI analgesia for MRF patients after SSRF operation. Our discovery warrants further investigations in order to compare the observed pain-relieving effect of EGCG with other analgesia techniques.

Disclosure statement

The authors declare that they have no conflict of interest.

Funding

The study was supported by the Quanzhou Science and Technology Project [2019N1055].

References

Ali-Osman F, Mangram A, Sucher J, Shirah G, Johnson V, Moeser P, Sinchuk NK, Dzandu JK. 2018. Geriatric (G60) trauma patients with severe rib fractures: is muscle sparing minimally invasive thoracotomy rib fixation safe and does it improve post-operative pulmonary function? Am J Surg. 216(1):46–51.

Althausen PL, Shannon S, Watts G, Thomas K, Bain MA, Coll D, O’Mara TJ, Bray TJ. 2011. Early surgical stabilization of flail chest with locked plate fixation. J Orthop Trauma. 25(11):641–647.

Brasel KJ, Moore EE, Albrecht RA, deMoya M, Schreiber M, Karmy-Jones R, Althausen PL, Shannon S, Watts C, Thomas K, Bain MA, Coll D, O’Mara TJ, Bray TJ. 2011. Early surgical stabilization of flail chest with locked plate fixation. J Orthop Trauma. 25(11):641–647.

Brown SD, Walters MR. 2012. Patients with rib fractures: use of incentive spirometry volumes to guide care. J Trauma Nurs. 19(2):89–91, quiz 92–83.

Choi JI, Kim WM, Lee HG, Kim YO, Yoon MH. 2012. Role of neuronal nitric oxide synthase in the antiangiogenic effects of intrathecal EGCG in a neuropathic pain rat model. Neurosci Lett. 510(1):53–57.

Chou SS, Sena MJ, Wong MS. 2011. Use of SternaLock plating system in acute treatment of unstable tricular sternal fractures. Ann Thorac Surg. 91(2):597–599.

Chou YP, Kuo LC, Soo KM, Tarng YW, Chiang HI, Huang FD, Lin HL. 2014. The role of repairing lung lacerations during video-assisted thoracoscopic surgery evacuations for retained haematothorax caused by blunt chest trauma. Eur J Cardiothorac Surg. 46(1):107–111.

Feng H, He Z, Twomey K, Illaldinov AW, Leong D, Wang Y, Li J, Gonzalez D, Sun HB. 2019. Epigallocatechin-3-gallate suppresses pain-related and proinflammatory mediators in the subcutaneous bursa in rotator cuff tendinopathy. Discov Med. 27(147):63–77.

Fraser SF, Tan C, Kuppusamy MK, Gukop P, Hunt JJ. 2017. The role of a video-assisted thoracic approach for rib fixation. Eur J Trauma Emerg Surg. 43(2):185–190.

Fusco F, Scimia P, Di Carlo S, Testa A, Luciani A, Petrucci E, Marinangeli F. 2017. Ultrasound-guided serratus plane block and fast-track tracheal extubation in the operating room for thoracic trauma patients: a case report. A A Case Rep. 9(11):305–307.

Galvagno SM, Jr., Smith CE, Varon AJ, Hasenboehler EA, Sultan S, Shafer G, To KB, Fox AD, Alley DE, Dittel M, et al. 2016. Pain management for blunt thoracic trauma: a joint practice management guideline from the Eastern Association for the Surgery of Trauma and Trauma Anesthesiology Society. J Trauma Acute Care Surg. 81(5):936–951.

Granetzny A, Abd El-Aal M, Emam E, Shalaby A, Böseila A. 2005. Surgical versus conservative treatment of flail chest. Evaluation of the pulmonary status. Interact Cardiovasc Thorac Surg. 4(6):583–587.

Haenel JB, Moore FA, Moore EE, Sauaia A, Read RA, Burch JM. 1995. Extraperitoneal bupivacaine for amelioration of multiple rib fracture pain. J Trauma. 38(1):22–27.

Ho AM, Karmakar MK, Critchley LA. 2011. Acute pain management of patients with multiple fractured ribs: a focus on regional techniques. Curr Opin Crit Care. 17(4):323–327.

Karmakar MK, Ho AM. 2003. Acute pain management of patients with multiple fractured ribs. J Trauma. 54(3):615–625.

Krupkova O, Sekiguchi M, Klason J, Hausmann O, Konno S, Ferguson SJ, Wueest T, Koak K. 2014. Epigallocatechin-3-gallate suppresses interleukin-1β-induced inflammatory responses in intervertebral disc cells in vitro and reduces radiculopathic pain in rats. Eur Cell Mater. 28:372–386.

Kuang X, Huang Y, Gu HF, Zu YX, Zou WY, Song ZB, Guo QL. 2012. Effects of intrathecal epigallocatechin gallate, an inhibitor of Toll-like receptor 4, on chronic neuropathic pain in rats. Eur J Pharmacol. 676(1–3):51–56.

Lafferty PM, Anavian J, Will RE, Cole PA. 2011. Operative treatment of chest wall injuries: indications, technique, and outcomes. J Bone Joint Surg Am. 93(8):97–110.

Li Q, Zhang X. 2015. Epigallocatechin-3-gallate attenuates bone cancer pain involving decreasing spinal tumor necrosis Factor-α expression in a mouse model. Int Immunopharmacol. 29(2):818–823.

Liao S, Kao YH, Hiipakka RA. 2001. Green tea: biochemical and biological basis for health benefits. Vitam Horm. 62:57–83.

Nirula R, Shahrahmani N, Mardani G. 2018. The effect of green tea ointment on episiotomy pain and wound healing in primiparous women: a randomized placebo-controlled trial. J Pain Res. 325(1):14–22.

Olland A, Puyraveau M, Guinard S, Falcoz PE, Massard G. 2019. Surgical stabilization for multiple rib fractures: whom the benefit—a prospective observational study. J Thorac Dis. 11(S2):S130–S140.

Pieracci FM, Majercik S, Ali-Osman F, Ang D, Dober A, Edwards JG, French B, Gasparri M, Marasco S, Minshall C, et al. 2017. Consensus statement: surgical stabilization of rib fractures rib fracture colloquium consensus clinical practice guidelines. Injury. 48(2):307–321.

Shahrahmani H, Karimian N, Jannesari S, Rafieian-Kopaei M, Mirzaei M, Ghahandari S, Shahrahmani N, Mardani G. 2018. The effect of green tea ointment on episiotomy pain and wound healing in primiparous women: a randomized, double-blind, placebo-controlled clinical trial. Phytother Res. 32(3):522–530.

Shen CL, Yeh JK, Cao JJ, Wang JS. 2009. Green tea and bone metabolism. Nutr Res. 29(7):437–456.

Solberg BD, Moon CN, Nissim AA, Wilson MT, Margules DR. 2009. Treatment of chest wall implosion injuries without thoracotomy: techniques healing of femoral bone defect. Phytomedicine. 55:165–171.