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Research article

Topical lyophilized thrombin application improves wound healing for posterior spinal surgery

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ABSTRACT

Background: The erector spinae plane block (ESPB) was proposed as a part of the postoperative multimodal analgesic regimen to improve pain management after posterior spinal surgery. However, ESPB might cause more surgical incisional wound exudate and poor wound healing, which might be improved after topical lyophilized thrombin application.
Materials and methods: We performed a retrospective study on patients who received posterior spinal surgery between January 2018 and December 2021. These patients were assigned into three groups: group A (general anesthesia), group B (general anesthesia with ESPB), and group C (general anesthesia with ESPB and topical 1000-unit thrombin application). Postoperative outcomes, including times of dressing changes, duration of suture removal, and incisional wound healing, were compared among these groups.
Results: Our study included 89 patients, with 48, 20, and 21 patients in groups A, B, and C, respectively. Baseline demographics, height, weight, comorbidities, and operation duration were comparable among the three groups. Group B required statistically significantly more dressing changes and had a prolonged duration of suture removal than group A (9.4 ± 4.7 versus 6.5 ± 2.0 times, 16.2 ± 3.7 versus 14.2 ± 1.4 days, respectively), which could be statistically significantly improved after the thrombin application in group C. Group B also had more frequent poor wound healing (25.0 %), which could also be improved after the thrombin application (0.0 %).
Conclusions: ESPB could cause more dressing changes and poor surgical wound healing after posterior spinal surgery, which could be improved by topical lyophilized thrombin powder application.

1. Introduction

The erector spinae plane block (ESPB) is a relatively novel regional anesthetic procedure proposed by Forero et al., in 2016 [1]. A local anesthetic is injected into the interfascial plane below the erector spinae muscle to manage acute or chronic pain in the thoracic and lumbar areas [2]. Randomized clinical trials have demonstrated that ESPB could decrease postoperative pain intensity and opioid consumption and improve postoperative recovery in spinal surgery patients [3–5]. In addition, the ESPB procedure is easy to perform with a low incidence of complications [6]. Therefore, ESPB was proposed as a part of the multimodal analgesia to improve pain

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management during the perioperative period in spinal surgery [7].

It was reported that ESPB had a low incidence of complications, including sensory, motor, hematologic, and adverse hemodynamic outcomes, or nausea and vomiting [8,9]. However, during our clinical practice, we found that, in our patients who received the ESPB during the posterior spinal operation for spinal fusion or decompression, although they had improved pain relief and consumed less amount of anesthetics, they also had an excessive amount of exudate from the surgical wound after the operation. During the wound healing process, the appropriate amount of exudate can provide a moist environment to promote wound healing, whereas over-production of exudate at the surgical site could cause patient discomfort, delay the wound healing process, and increase the risk of infection [10–12]. We found no prior research on wound exudate and its management following the ESPB procedure during posterior spinal surgery.

Thrombin is a serine protease and can regulate hemostasis [13]. Animal and clinical studies have demonstrated that thrombin-containing materials could improve surgical wound healing [14–17]. In a randomized controlled clinical trial, Ma et al. reported that the topical application of a thrombin-containing matrix (Surgiflo) could successfully reduce the postoperative bleeding and amount of wound drainage after the posterior lumbar surgery [18]. In the clinic practice, we applied the lyophilized thrombin powder topically in patients who received the ESPB procedure during the posterior spinal fusion or decompression operation. We thought the lyophilized thrombin powder spray could significantly reduce the wound exudate and improve wound healing. This application approach was not reported earlier.

Therefore, we performed the present retrospective study in patients who received posterior spinal surgery under general anesthesia with or without ESPB and topical application of thrombin powder to provide a treatment choice to manage the surgical wound exudate and improve the healing process after the posterior spinal surgery.

2. Material and methods

2.1. Study design and participants

This was a retrospective cohort study of patients who received posterior spinal surgery at the Weiyi Orthopedic Hospital, Chongqing, China, between January 2018 and December 2021. The study protocol was approved by the hospital ethics committee. The informed consent was waived due to the retrospective study design.

The participant inclusion criteria were patients 1) $\geq$18 years old, 2) hospitalized for the spinal fusion or decompression, or corrective spinal deformity surgery through the posterior approach, 3) undergoing the general anesthesia, with or without ESPB and topical application of lyophilized thrombin during the operation, and 4) with class I surgical incision. The exclusion criteria were patients with 1) local or generalized anesthesia combined with intrathecal anesthesia or 2) incomplete medical records.

2.2. Surgical operation, ESPB, and topical application of thrombin

The same team of orthopedic surgeons performed all the posterior spinal operations following the standard surgical steps. The same team of anesthesiologists also performed general anesthesia. In addition, one anesthesiologist licensed in the Duplex ultrasound performed the ultrasound-guided ESPB procedure by injecting 0.5 % ropivacaine (Jiabo Pharmaceutical Co., Ltd., Guangzhou, China) under the fascia of the erector spinae muscle in the sagittal plane and at the level of the tip of the transverse process. The volume of 0.5 % ropivacaine was 15 ml on each paraspinal side for spinal surgery on 2–3 vertebrae, with an additional 5 ml for each additional 1–2 vertebrae. After the surgical operation and before the wound closure, some patients received the topical spray of 1000 units of lyophilized thrombin powder (Leiyunshang Pharmaceutical Co., Ltd., Changchun, China).

2.3. Data collection and group assignments

Medical records were reviewed to document the demographics (sex and age), weight, height, comorbidities (hypertension, diabetes, and hypoalbuminemia), duration of operation, times of dressing change until the wound healed, postoperative days of suture removal, and complete wound healing.

The included patients were assigned into three groups. Group A were patients who received general anesthesia. Group B received general anesthesia with the ESPB procedure, and group C received general anesthesia with the ESPB procedure and topical thrombin spray.

2.4. Outcome measurements

The study outcomes were the surgical incisional wound healing status, including 1) times of postoperative wound dressing changes. Our routine practice was to change the dressing once on the first postoperative day and once every two days afterward. The more times of wound dressing changes could indirectly suggest a slow wound healing process since a wound with excessive exudate or infection commonly requires more times of dressing changes. 2) postoperative duration until suture removal. Most sutures on the class I incisions in our hospital were removed 10–14 days after the operation. We defined the time of suture removal $\geq$16 days as a prolonged duration until suture removal. 3) poor incisional wound healing. We defined any wound-associated complications, including incisional wound superficial or deep infection and wound dehiscence, as poor wound healing [19]. We reviewed the medical records up to one year after the surgical operation to examine the surgical wound healing in these patients.

2.5. Statistical analysis

The continuous data are presented as mean ± standard deviation or median with interquartile range and compared by the ANOVA or Kruskal–Wallis test, depending on the normality test. The categorical data are presented as numbers with percentages and are compared using the Chi-square analysis. A $P < 0.05$ was considered statistically significant. The Bonferroni method for the P value corrected the pairwise comparisons among the three groups. A $P < 0.05/3$ was considered statistically significant. All statistical analyses were conducted by Shanghai Eryun Information Technology Co., Ltd. using SPSS software (version 22.0, IBM, Armonk, New York, USA).

3. Results

3.1. Patient characteristics

Our study included 89 patients, with 48, 20, and 21 in groups A, B, and C, respectively. The baseline demographics, weight, height, body mass index, comorbidities, and duration of operation were comparable among the three groups (Table 1).

3.2. Outcome comparisons

Outcome comparisons showed statistically significant differences in the times of dressing changes and the postoperative duration of suture removal among the three groups (Table 2). Group B had more dressing changes (statistically significant) compared with groups A and C. Group B also required a longer duration before the suture removal than groups A and C. There were no statistically significant differences in the times of dressing changes and the duration of suture removal between groups A and C. Further analysis showed that more patients in group B had suture removal ≥16 days postoperatively. All this evidence suggested that the ESPB procedure during the general anesthesia could delay the surgical wound healing, probably due to the excessive wound exudate in patients undergoing posterior spinal surgery. The topical application of lyophilized thrombin powder could reverse the excessive wound exudate and delay wound healing.

Regarding surgical incisional wound healing status (Table 2), there was no statistically significant difference in the number of patients with poor incisional healing between groups A and B and between groups A and C. However, group C had a statistically significant lower percentage of patients with poor incisional healing than group B, suggesting that the topical application of lyophilized thrombin powder could significantly improve the incisional healing, even if the ESPB procedure did not significantly change the incisional healing after the general anesthesia. In addition, out of 11 patients with diabetes, only 2 patients with diabetes had poor wound healing, which happened in group B.

Fig. 1A–C illustrates a patient in group B who had increased exudate after the ESPB procedure and required frequent dressing changes. The surgical wound finally healed with scars. Fig. 1D shows the topical application of 1000-unit thrombin powder in a patient in group C.

4. Discussion

The ESPB is a relatively novel procedure for adequate pain control in the thoracic and lumbar areas [2]. It provides satisfactory and safe analgesia in patients after spinal surgery [7]. However, our clinical experience found that patients undergoing the ESPB procedure had increased surgical site exudates and poor healing processes, which were not reported earlier. This retrospective study revealed that when compared to patients undergoing general anesthesia, patients undergoing additional ESPB procedures required more wound dressing changes, a longer time to suture removal, and had more frequent poor incisional healing, all of which could be statistically significantly improved by the topical application of lyophilized thrombin powder. Diabetic patients could have poor wound healing. Here, we showed that poor wound headling in diabetic patients was observed only in patients undergoing ESPB procedure, but not

Table 1
Baseline characteristic comparisons among three groups.

Characteristics	Group A (N = 48)	Group B (N = 20)	Group C (N = 21)	*P*
Sex, N (%)				0.889
Male	24 (50.0)	9 (45.0)	11 (52.4)	
Age, year	54.4 ± 13.2	56.1 ± 22.0	62.2 ± 11.0	0.146
Height, cm	160.9 ± 7.1	160.5 ± 9.5	161.4 ± 7.7	0.928
Weight, kg	61.6 ± 10.3	62.0 ± 10.8	60.2 ± 10.0	0.837
Body mass index, kg/m^2	23.7 ± 3.7	23.9 ± 3.0	23.1 ± 3.1	0.681
Comorbidities, N (%)				
Hypertension	13 (27.1)	11 (55.0)	9 (42.9)	0.078
Diabetes	3 (6.2)	5 (25.0)	3 (14.3)	0.110
Hypoalbuminemia	4 (8.3)	1 (5.0)	2 (9.5)	0.841
Duration of operation, min	185.2 ± 73.3	201.6 ± 112.0	207.3 ± 88.9	0.568

Data are presented as mean ± standard deviation unless otherwise stated.

Table 2
Outcome comparisons among three groups.

Outcomes	Group A (N = 48)	Group B (N = 20)	Group C (N = 21)	*P*
Dressing changes, time	6.5 ± 2.0	9.4 ± 4.7*	5.7 ± 1.0	<0.001
Duration to suture removal, days	14.2 ± 1.4	16.2 ± 3.7*	13.8 ± 1.2	0.001
Duration to suture removal, N (%)				0.038
<16 days	44 (91.7)	14 (70.0)	20 (95.2)	
≥16 days	4 (8.3)	6 (30.0)	1 (4.8)	
Poor incisional wound healing, N (%)	3 (6.2)	5 (25.0)†	0 (0.0)	0.012

Data are presented as mean ± standard deviation unless otherwise stated.
Two group comparisons show significant differences between group B and group A or C (*), between group B and C (†).

those with thrombin powder application. A study like this has never been reported before.

Surgical incisional wound healing is a complex process that can be affected by many internal and external factors [20]. It involves the activation of the coagulation cascade and the infiltration of immune cells into the wound, which not only helps to defend against pathogenic invasion but also promotes wound repair [21]. The physiology of incisional wound healing includes several consecutive and overlapping phases, such as hemostasis, inflammation, proliferation, re-epithelialization, and remodeling [22]. Immediately after the surgical trauma, tissue damage, and vascular rupture can lead to platelet activation and aggregation, as well as the release of various stimulating and growth factors that recruit inflammatory response cells and promote tissue regeneration. Meanwhile, neutrophils, monocytes, fibroblasts, and endothelial cells are deposited in the fibrin scaffold following platelet activation. At the site of tissue injury, migrated neutrophils can activate monocytes and macrophages to remove necrotic tissue cells and release cytokines and growth factors that promote fibroblast proliferation, vascular growth, and epidermal cell migration into the proliferative phase. The final phase of wound repair includes tissue remodeling, which begins 2–3 weeks after the initial surgical injury and lasts for a year or more, depending on the severity of the wound [23]. In addition, collagen deposition is a major process of wound repair, which determines the elasticity and strength of the repaired tissue [24].

Wound exudate is the liquid discharge from the wound. Surgical incisional wound exudate mainly consists of water, nutrients, electrolytes, blood cells, inflammatory cytokines, enzymes, and growth factors [25]. At the beginning of the surgical incisional healing process, there may be a small amount of exudate after suturing due to tissue necrosis and blood leakage through the damaged vessels. The exudate can be a double-edged sword in the healing process of a surgical incisional wound [10]. A moderate amount of exudate can deliver various nutrients and growth factors to the wound to promote healing and tissue growth. However, excessive exudate can also lead to local edema, increase local tissue pressure, and reduce blood circulation and oxygen supply. In addition, the enzymes in the exudate not only degrade necrotic tissues but also injure the surrounding normal tissues. All of these can cause delayed wound healing. Common causes of excessive exudate from the surgical incisional sites include capillary leakage due to inflammatory response, impaired lymphatic return, venous stasis, increased venous pressure, and hypoproteinemia from poor nutrition. Clear, thin, and odorless exudate is usually without infection. When an exudate has an infection, it can have different colors and odors and is often viscous. Culture can be performed to identify possible pathogens [26].

Our present study showed that patients with the ESPB procedure had increased times of dressing changes due to increased exudate from the surgical site. This increased exudate was not due to infection because there were no signs of fever, increased white blood cell count, and elevated C-reactive protein and procalcitonin levels in these patients. The exact mechanism of increased exudate after the ESPB procedure is unknown. It might be due to the serum leakage from the increased hydrostatic pressure in the constricted blood vessels after the ESPB procedure, as ropivacaine injected during the ESPB was reported to have vasoconstrictive effects [27,28]. A high volume of ropivacaine (≥15 ml) could also cause local swelling and edema, which delayed the interstitial fluid absorption and caused a prolonged exudate discharge.

Thrombin is a serine protease. In the human body, thrombin is converted from the synthesized prothrombin and secreted into the circulation by the liver after being activated by the endogenous and exogenous coagulation pathways [13]. In addition to converting soluble plasma fibrinogen into insoluble fibrin clots, promoting platelet aggregation, and participating in the coagulation cascade, thrombin can have several other essential functions, including initiating mitosis in endothelial cells, fibroblasts, and smooth muscle cells, promoting the production and secretion of extracellular matrix proteins, and influencing the connective tissue remodeling process [29]. Thrombin is involved in repairing normal tissues and blood vessels and forming new endothelium after certain acute and chronic pathological conditions, including vascular injury, atherosclerosis, pulmonary fibrosis, and glomerulonephritis. The functions of thrombin are mediated through its protease-activated receptors, a family of G protein-coupled receptors that initiate the cellular signaling to stimulate biological effects and have an essential role in proliferation, migration, and cell differentiation involved in the early stages of wound healing. Thrombin can also promote vasoconstriction through endothelial regulatory mechanisms [30]. Several clinical trials have evaluated the efficacy of thrombin-containing materials during surgical wound healing. Ma et al. and EI-Fattah et al. tested a thrombin-based hemostatic material (Surgiflo) in surgical patients separately. Both research groups showed that this material could successfully accelerate wound healing [16,18]. A meta-analysis that included six clinical trials reported another topical thrombin-based hemostatic agent (Floseal) that could also decrease the amount of bleeding and improve wound healing after total knee arthroplasty [31].

The lyophilized thrombin powder was applied topically to the surgical wound after posterior spinal surgery in the current study. Lyophilization is preferred to maintain protein activity during drug development [32]. Previous case studies have used lyophilized thrombin powder to facilitate the treatments in patients with aneurysms [33,34]. In our study, we directly sprayed the lyophilized

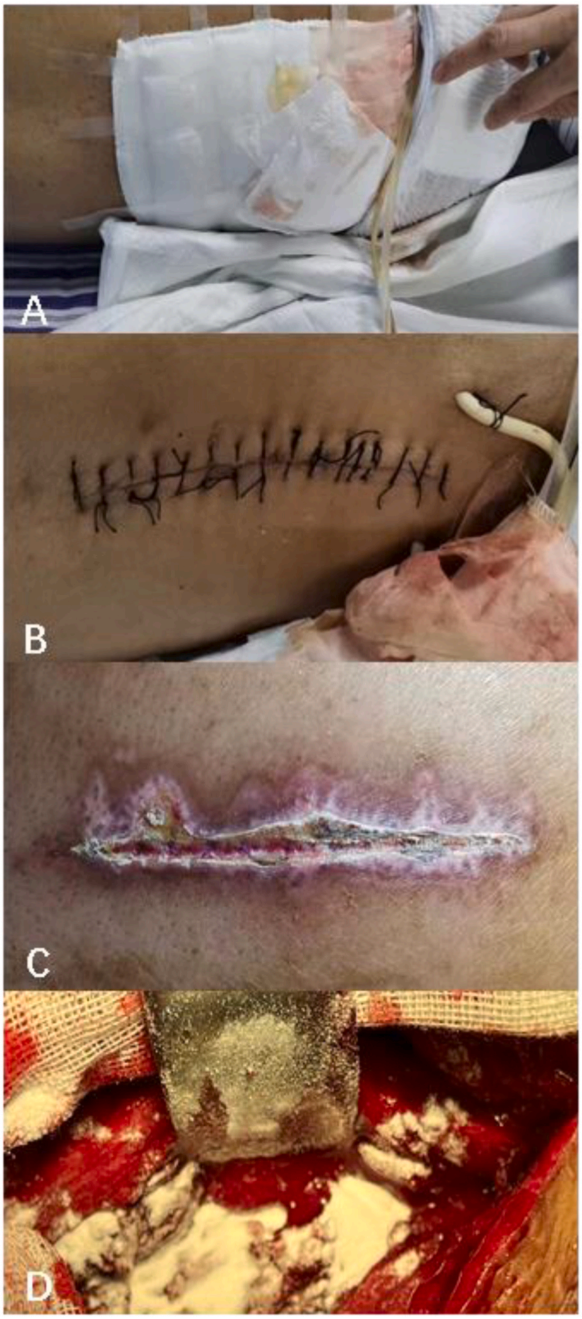

Fig. 1. **A-C,** A patient in group B who received the ESPB procedure during the spinal posterior surgery. **A**) excessive exudate that required frequent dressing changes. **B**) poor surgical incisional wound healing. **C**) Delayed suture removal with scars. **D)** topical application of 1000-unit thrombin powder in group C patients.

thrombin powder into the surgical wound, where it was dissolved in the exudate and converted into thrombin by the extrinsic activating pathway. We demonstrated that the local application of lyophilized thrombin powder could decrease the requirements for dressing changes and shorten the duration of suture removal after the ESPB procedure. Patients undergoing topical thrombin application also had better incisional wound healing. Thrombin might have a local vasoconstrictive effect to reduce exudate [30]. In addition, thrombin might stimulate tissues and cells to release various growth factors to participate in angiogenesis and tissue repair to promote wound healing [35]. The exact wound-promoting effects of thrombin require further studies.

One special notice in our study was that group B had more patients with diabetes than the other two groups. Diabetes is a well-known risk factor for poor wound healing and complications. However, the poor wound healing in group B could not be solely attributed to diabetes because detailed analysis showed that not every patient with diabetes had poor wound healing. Most patients with poor wound healing had no diabetes.

The limitations of our study included its small sample size and single-center investigation. Its retrospective design also carried intrinsic biases. For example, the outcome measurements, such as the number of dressing changes and wound healing status, were obtained from the medical records, which might have missing or biased information. In addition, in this retrospective study, we could not consider the influences of many confounders, such as patient baseline health status, perioperative antibiotic use, and physician experience. However, our present research was the first to investigate surgical wound healing after the ESPB procedure and to observe the effect of topical thrombin application on surgical wound healing. Future multi-center prospective clinical trials are required to confirm our findings.

The ESPB procedure could cause more dressing changes, delayed suture removal, and poor incisional healing in patients undergoing posterior spinal surgery. Topical application of lyophilized thrombin powder could improve these changes and promote incisional wound healing. Further studies are warranted.

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Data availability statement

Data are available upon reasonable request to the corresponding author.

Ethics approval

The study protocol was approved by the Ethics committee of Guiqian International General Hospital (approval number: 2023[05]).

CRediT authorship contribution statement

Yinjie Zhao: Writing – review & editing, Data curation. **Ming Liu:** Writing – review & editing, Data curation. **Wenyao Li:** Writing – review & editing, Formal analysis. **Guocai Tao:** Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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