Chin J Integr Med 2019 Jul;25(7):554-560

Chinese Journal of Integrative Medicine

Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Review

Tetramethylpyrazine Improves Postoperative Tissue Adhesion: A Drug Repurposing*

YAN Shuai[1], YUE Yin-zi[1], ZONG Yang[1], and ZENG Li[2]

ABSTRACT Plants are known to possess plenty of pharmacological activities as a result of various phytoconstituents. Tetramethylpyrazine (TMP), one of the most widely used medicinal compound isolated from traditional Chinese herb, is usually employed for anti-oxidation, anti-inflammation, anti-platelet aggregation, anti-lipid, anti-fibrosis, as well as activating blood, removing stasis, dilating small arteries, improving microcirculation and antagonizing calcium. In the present paper, the anti-adhesion effect of TMP were reviewed. TMP was found to play a multi-target and muti-link role in anti-adhesion by inhibiting hyperplasia of collagen and overexpression of adhesion-related factors and reducing the concentration of white blood cells and fibrin in plasma. Because previous studies mostly focused on *in vitro* experiments and animal experiments, there is an urgent need for clinical research with abundant indicators to further prove its anti-adhesion potency. Future basic research should concentrate on the development of TMP as a biological material.

KEYWORDS tetramethylpyrazine, tissue adhesion, pharmacological activity, review

Chinese medicine, which was practiced for centuries to treat various diseases, has aroused global concern in recent years, and Chinese herbal extracts used as therapeutic and cytoprotective agents are drawing increasing attention. Many attempts have been made to collect data by researches on extract of Chinese hebal formula, single herb and single compounds of Chinese herbs, according to orthodox pharmacological activities.

Although the development of modern medicine advances the application of trauma surgery and minimally invasive surgery in most clinical departments, trauma and surgery, both of which may damage tissue, indeed increase the incidence of tissue adhesion, thus imposing economic and spiritual burdens on the patients. Chinese herbs are also screened based on neuroprotective functions to develop alternative therapies for tissue adhesion.

Rhizoma chuanxiong is a traditional Chinese herb firstly recorded in *Shen Nong's Classic of the Materia Medica* (Shen Nong Ben Cao Jing). Being a perennial herbal plant of the Umbelliferae, it is acrid and slightly bitter in flavor, mild in nature, and mainly manifests its therapeutic actions in tonifying qi and activating blood, relieving depression and pain. Tetramethylpyrazine (TMP), an alkaloid extracted from *Rhizoma chuanxiong* , is one of its active composition. Its monomer originally withdrawn in 1970 can be synthesized now. Thanks to multiple pharmacological effects, such as activating blood and removing stasis, dilating small arteries, improving microcirculation as well as anti-lipid oxidation, anti-platelet aggregation, antagonizing calcium and anti-fibrosis,[1] TMP is widely used for the treatment on cerebral vascular diseases,[2] pulmonary hypertension,[3] chronic renal failure,[4] liver cirrhosis[5] and radioactive pulmonary fibrosis.[6] In addition, a wide range of dosages and few side effects are attributive to its clinical application.[7] Growing clinical indications of TMP lighten researchers at home and abroad to investigate its repair to adhesion after trauma.[8] As shown in Table 1, TMP is reported to prevent postoperative adhesion, as it is involved in the anti-inflammatory response, inhibits fibroblast mitosis and proliferation as well as reduces the

*Supported by the National Natural Science Foundation of China (No.81804098, 81673982), Natural Science Foundation of Jiangsu Province (No. BK20180219), Young Talents in Jiangsu Province (No. QNRC2016255) and Youth Project of Suzhou Traditional Chinese Medicine Hospital (No. YQN2016003)

1. Department of Anorectal Surgery, Suzhou Hospital of Traditional Chinese Medicine, Suzhou (215009), Jiangsu Province, China; 2. First College of Clinical Medicine, Nanjing University of Chinese Medicine, Nanjing (210023), China
Correspondence to: Prof. ZENG Li, Tel: 86-25-85811788, E-mail: zengbingli@163.com

DOI: https://doi.org/10.1007/s11655-018-3021-3

fibroblast DNA and collagen synthesis.[2-9] But further studies are required to distinguish variations in the possible mechanisms. Accordingly, the present paper summarized the physical and chemical properties, chemical compositions, as well as its anti-adhesion ability of TMP to extend its clinical application.

Literature Search Strategy

Articles published before October 2017 in databases including PubMed, EMBase, MEDLINE, Cochrane Library, CINAHL, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Medicine (CBM), VIP Journal Integration Platform and Wanfang Data were retrieved by using terms "tetramethylpyrazine" AND "adhesion"; or "ligustrazine" AND "adhesion". The results were merged by reference management software in which the duplicate records were removed. Inclusion and exclusion criteria are listed as follows: (1) Participants: patients or animals with adhesion were included; (2) Intervention: both oral and injection dosage were included; acupuncture, massage and other Chinese medical therapies were excluded; (3) Literature: randomized controlled trials (RCTs), observational studies, case reports and basic researches were included; systematic review, abstracts, editorials, letters and expert opinions were excluded. (4) Language: all the articles included were written in English or Chinese. Three authors reviewed the title of each article individually, as well as the full text if necessary. All articles were selected and conferred to make a final decision according to predefined inclusion and exclusion criteria.

Physical and Chemical Properties

TMP is colorless needle crystal with a special smell and hygroscopicity. Its melting point is 80–82 ℃, boiling point is 190 ℃. It is highly soluble in hot water and petroleum ether, soluble in chloroform and dilute hydrochloric acid, slightly soluble in ether, and insoluble in cold water.[10] TMP can be extracted from *Rhizoma chuanxiong* or by artificial synthesis. Its molecular formula is $C_8H_{12}N_2$, weighing 136.20. The mother nucleus of TMP is the pharmacophore, and the 4 linking substituents mainly affect its absorption, distribution, metabolism and excretion. Therefore, pyrazine ring remaining unchanged, the biological activity can be improved by modifying the structure of side chains and drugs with high efficiency and low toxicity are thus gained. Currently, TMP sold on the market is mainly in the form of saline solution, such as TMP hydrochloride and ligustrazine phosphate. The former possesses lower melting point.

Clinical Study

Postoperative Tendon Adhesion

Hand injuries often lead to tendon rupture which then forms varying degrees of adhesion that causes hand dysfunction. This is a chronic problem with high incidence, and male is the majority.[11] Normal anatomy shows tissues around tendons. But the hyperplasia of tendon and the tissue in the peritendon area in postoperative repair will produce postoperative tendon

Table 1. Pharmacology, Molecular Targets and Clinical Application of TMP

Pharmacology	Molecular targets	Clinical application
Protecting vascular endothelial cells and anti-oxidant	Suppresses vasoconstriction produced by ET-1 and induces a significant decrease in plasma ET-1 levels, prevents intracellular ROS generation and scavenge ROS and inhibits NF-κB activation through ERK1/2 and p38 signaling pathways	Cardiovascular diseases
Improving bloodrheology, inhibiting platelet aggregation and reducing fibrosis	Inhibited PDGF-βR pathway and NLRP3 inflammasome expression, decreased abundance of TIMP-1 and TIMP-2 and promoted the expression of MMP-2 and MMP-9	Liver fibrosis
Protecting neuronal cells from oxidative stress-induced retinal damage	Inhibition of iNOS expression and leukostasis and suppression of ROS formation, mitochondrial dysfunction and blockade of MAPKs phosphorylation	Diabetic retinopathy
Exhibited potent immunomodulatory and anti-inflammatory	Suppressed lymphocyte and eosinophil mobilization, and reduced cytokine IL-5 and IL-13 production	Allergic asthma
Anti-inflammatory	Inhibition of NF-κB and ICAM-1 expression	Acute lung injury
Decreased the levels of IL-β1, IL-6, TNF-α and TGF-β1, attenuated TGF-β1-induced upregulation of FN and CTGF	Inhibiting inflammation and regulating the TGF/Smad signaling pathway	Abdominal adhesions

Notes: ET-1: endothelin; ROS: reactive oxygen species; PDGF-βR: platelet-derived growth factor-β receptor; NF-κB: nuclear factor-kappa B; ERK1/2: extracellular regulated protein kinases 1/2 ; NLRP3: LRR and pyrin-domain-containing protein 3; TIMP-1: tissue inhibitor of metalloproteinase 1; TIMP-2: tissue inhibitor of metalloproteinase 2; MMP-2: matrix metalloproteinase 2; MMP-9: matrix metalloproteinase 9; MAPKs: mitogen-activated protein kinases; ICAM-1: intercellular cell adhesion molecule-1; CTGF: connective tissue growth factor

adhesion (PTA), which prevents the recovery of the function of gliding joints.[12] Studies found that TMP Injection had been used for the patients whose fingers were cut by sharp instrument.[13,14] Shen, et al[14] selected 47 patients from the hospitalized patients who cut the fingers by sharp instruments. The result revealed that TMP significantly increased the total activity measurement percentage of the affected /tendon side, the flexion and extension degree of the joint, and the total range of active movement and improved the functional activity of finger flexion within 5 to 6 months.

Local administration of sodium hyaluronate (HA) and chondroitin sulfate (CS) combinations are often found in PTA treatment.[15] However, certain fluidity restricted the period that herbal extract and polymer gel remain around the injured tendon, and the texture and applied area of membrane barrier occasionally impede it completely fitting the suture. TMP Injection and Danhong Injection (丹红注射液) can be used with absorbable bio-membranes, and their combination is superior to single membrane in active degree of tendon and dexterity of hand. Accordingly, TMP Injection further improved the therapeutic effect by activating blood and resolving stasis accompanied with absorbable bio-membrane. Although a lack of research is undeniable, the retention time of once injection into the membrane is unknown, the safety of their combination still needs more cases to observe.

Postoperative Epidural Adhesion

After spinal surgery like lumbar disc herniation, the scar tissue formed by fibrous ring of intervertebral disc causes adhesion of spinal dura mater to nerve root, resulting in failed back surgery syndrome (FBSS) and surgical failure.[16] Wang, et al[17] reported HA and TMP mixture can effectively prevent epidural adhesion after lumbar intervertebral disc herniation. After 12–36 months of follow-up, intermediate follow-up data was available for 352 patients. The scoring system for low back pain from Japanese Orthopedics Association (JOA) was applied in the evaluation of curative effect for quantitative marking and calculation of the improvement rate. Research showed that the miscible liquid of TMP and HA instantly fosters steady and enduring outcomes when it is used to prevent the formation of the adhesive scars on the epidural after the operation of lumbar disc protrusion. It is possibly linked with the 3-dimensional protective screen that is shaped by HA around the nerve roots after the surgery. Lubrication can guard the nerve roots with surrounding tissues. However, as the HA is continuously degraded and absorbed by body itself, the effect of the protective screen fades away; while at the same time, the TMP has gradually restrained the synthetize of fibrocyte DNA, reduced the collagen type Ⅰ and Ⅱ of the fibrocyte in the scars, controlled the growth factor (GF) in the formation of scars, which result in the distinct effects.

Postoperative Abdominal Adhesion

Abdominal adhesion refers to the pathologic adhesion zone between the surface of abdominal organs formed during repair of peritoneal trauma, which can be either a fine connective tissue membrane or a thick fibrous tissue bridge. A typical adhesion is formed on the damaged peritoneal surface; however, since normal mesothelial cells hardly cover, the damaged peritoneal surface may adhere to any tissue or organs it connects to, such as peritoneum, stomach, small intestine, large intestine and ovary. Postoperative abdominal adhesion (PAA) results in long-term chronic abdominal pain,[18] constipation,[19] intestinal obstruction[20] and even female infertility,[21] thus placing a heavy financial burden on the patient and social health resources. Wang, et al[22] assigned 72 patients with simple adhesive intestinal obstruction to routine treatment group and TMP group. The former group were fasted and performed with gastrointestinal decompression. Fluid refusion was applied to keep acid-base and water-electrolyte balance, and antibiotics and anti-acids were used properly. The patients in TMP group were given TMP Injection (120 mg/d) within 5% glucose solution (500 mL) for 4 days. The result indicated that TMP showed a remarkable anti-adhesion effect with PAA patients. Zhang, et al[23] randomly assigned 70 hospitalized patients who had undertaken abdominal operations for adhesive intestinal obstruction to anti-adhesion and control groups. The patients in the anti-adhesion group was perfused at the end of the operation with 40 mg TMP diluted with 250 mL saline and a built-in rubber drainage tube was set in the abdominal cavity which was temporarily closed and then opened 12–24 h after the operation. The patients in the control group was treated in the same way except the perfusion in the abdominal cavity. The results showed that after the intraperitoneal injection of TMP, the bowel sounds recovery time and first exhaust and defecation time in the anti-adhesion

group were significantly earlier than those patients in the control group. Long-term follow-up also indicated that the anti-adhesion group excelled the control group in the adhesive rate and overall curative effect, which proved that TMP promoted the recovery of gastrointestinal function after operation. Intravenous injection or TMP perfusion in the abdominal cavity are both effective in treating simple PAA. The mechanism may be related to the active pharmacology of TMP. It achieves anti-adhesion effect by improving the local blood transport, reducing inflammatory mediators around the adhesion of intestinal canal, cellulosic exudation to promote gastrointestinal peristalsis.

Experimental Study

PTA

Wei, et al[24] reported their observation of 24 cocks with injured toe deep flexor tendon treated with TMP gelatin membrane. The results demonstrated that TMP gelatin membrane could prevent tendon adhesion formation by sustained-release technology to maintain drug concentration on the injury. In addition, TMP Injection's action on the basic fibroblast growth factor (bFGF) in rat's tendon and peritendon area at different time points was observed. It was found that TMP Injection could inhibit the production of bFGF in the tissue around the tendon in gene transcription levels during recovery. Meanwhile, no side effects were observed on the tension of muscle tendon in the later stage, which ensured high security.[25] The team also reported that mRNA expression of type Ⅰ and Ⅲ collagen in epitendon and peritendon tissues decreased in the 1st and the 2nd week after postoperative injection of TMP. Because type Ⅰ and Ⅲ collagen in endotendon cells altered later than those in the epitendon and peritendon area, the injection failed to reduce collagen level in tendon parenchyma.[26] The above studies suggest that inhibition of collagen hyperplasia could effectively minimize PTA. Apart from anti-inflammation, double or multiple ways contribute to this process as well.

PEA

Wei, et al[27] established a postoperative epidural adhesion(PEA) model on New Zealand rabbits by removing lamina of L5 vertebra to observe the effect of TMP polyvinyl alcohol membrane on epidural adhesion. Results showed that TMP polyvinyl alcohol membrane applied significantly reduced both the area and density of the scar as well as the area of epidural space of the rabbits. It indicated that TMP polyvinyl alcohol membrane could prevent platelet aggregation and improve microcirculation, probably because polymer protected metallic colloid to prevent and treat dural adhesion after laminectomy. The conclusion is consistent with the findings of Chen, et al[28] who implanted TMP with autologous periosteum in place of the missing vertebral lamina of rats to prevent PEA. In summary, the inhibition of platelet aggregation is another principal mechanism of the treatment of PEA.

PAA

Peritoneal damage stimulates inflammatory cells to release cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6, which are considered extremely crucial for fibrogenesis.[29-31] These cytokines induce the release of plasminogen activator inhibitor (PAI)-1 and PAI-2 from mesothelial cells, which weaken the activity of plasminogen activators (PAs).[32,33] Transforming growth factor-β1 (TGF-β1) is also regarded as the primary fibrogenic and collagenic component in the inflammatory macrophages that infiltrate damaged tissue.[34] Zhang, et al[35] evaluated the effects of ligustrazine on the prevention of postoperative intra-abdominal adhesions in rats. They observed ligustrazine lowered the levels of IL-1β, IL-6 and TNF-α in serum, reduced the expression of TGF-β1 and connective tissue growth factor (CTGF) in the peritoneal fluid in a dose-dependent manner. The cell experiment concluded that ligustrazine dramatically attenuated TGF-β1 which induced upregulation of fibronectin (FN) and CTGF in peritoneal mesothelial cells (RPMCs) of rats. Meanwhile, ligustrazine significantly inhibited the expression of pSmad 2/3 and increased the level of Smad7 in rat RPMCs. Therefore, ligustrazine is probably applied to abdominal adhesion.[35] A study from Yan, et al[36] demonstrated that compared with the group treated by ligustrazine alone, TMP-nano-spray could effectively stabilize the balance of t-PA/PAI and reduce IL-1β level. In addition, cell experiment found TMP-nano-spray could inhibit TNF-α, stimulate over-expression of FN, TGF-β1 and CTGF in RPMCs and block TGF-β/Smad pathway to prevent abdominal adhesion.[37] The spray sets up a stable, efficient and convenient drug delivery system. It thus fills in a gap in traditional dosage form and provides a new perspective option for abdominal adhesion medication. Xu, et al[38] produced TMP thermosensitive sustained-release gel by themselves. They sprayed it on the model through

peritoneal cavity to evaluate its anti-abdominal adhesion ability by Nair score and immunohistochemistry. TMP thermosensitive sustained-release gel was proved to improve local microcirculation of adhesive intestines and activate collagenase in adhesive tissue. It also inhibited proliferation of type Ⅰ collagen, reduced collagen deposition, meanwhile promoted degradation and reabsorption of collagens. In order to observe TMP's effect on PAA rats, Zheng, et al[39] detected the expression of type Ⅰ, Ⅲ collagen, TNF-α and TGF-β1 in abdominal adhesion tissue after intraperitoneal injection of TMP. The results showed that TMP injection decreased the expression of type Ⅰ, Ⅲ collagen, TNF-α and TGF-β1 which might lead to prevent over-proliferation of peritoneal mesothelial cells and interfere with the formation of adhesion. Moreover, Shi, et al[40] prepared TMP hydrochloride microemulsion, for its satisfactory biodegradability and biocompatibility within the tissue, and observe its anti-abdominal adhesion potency. They found that low-dosage TMP hydrochloride microemulsion exhibited a best anti-adhesion effect, even superior to TMP injection, as it lowered collagen degree and contributed to maintain effective drug concentration. Although the above studies have not completely explained the mechanism of TMP's prevention and treatment of abdominal adhesion, it can be speculated that TMP regulated and controlled various growth factors and cytokines in different stages of abdominal adhesion and modified plasminogen activators so as to interfere with the occurrence of PAA.

PPA

Rapid development of cardiovascular surgery increases the number of patients receiving secondary cardiac surgery. However, many potentially problematic outcomes lurk in the operating procedure of a resternotomy in open-heart surgery, and many of them are due to potential adhesions in the pericardial cavity and retrosternal space.[41] Besides poor heart function, the most important complication after heart surgery is the adhesion of large blood vessels and pericardium adjacent tissue, which prolongs the duration of the surgery and increases the risk of cardiac and mediastinal injuries caused by thoracotomy.[42] Colak, et al[43] established a model of pericardial adhesion in domestic rabbits following Cliff method. Histological examination did not find pericardium and its outer membrane thickened, neither fibrous tissue proliferate in the TMP Injection group after modeling. However, specific mechanism was not discussed. Han, et al[44] established a rabbit PPA model to evaluate the protective effect of TMP Injection combined with HA on pericardium after cardiac surgery. The results suggested that HA and TMP could decrease the concentration of white blood cells (WBC) and fibrin in plasma to achieve anti-adhesive effect.

Thanks to more and more types of antibiotics, laparoscopic surgery and anti-adhesion methods, the incidence of postoperative adhesion has been reduced in recent years, although not completely controlled yet. Wherever the adhesion develops, organ or tissue dysfunction brought by the attachment and fixation of the adhesive tape always presents. Despite various anti-adhesion methods used in clinic, systematic study found that relevant treatment methods and medications, such as intraperitoneal isolation, intraperitoneal local hyaluronic acid, single anti-inflammatory and fibrinolytic agent that achieve satisfactory results in animal experiments, exhibit uncertain clinical efficacy, as they either act in large dose with more side effects and complications than benefits or inducing rejection. So far there are few any drug or treatment that can completely prevent abdominal adhesion, not to mention its clinic promotion. Therefore, to optimize anti-adhesive drug remains an important issue.

Pharmacological activities of TMP include dilating blood vessels, slightly lowering blood pressure, improving tissue microcirculation and blood perfusion, inhibiting aggregation and adhesion of platelet, preventing thrombus formation, preventing the proliferation of smooth muscle cells and fibroblast, regulating lipid metabolism, resisting lipid peroxidation and regulating immune function.[45] TMP plays a multi-target and multi-link role in tissue adhesion, because it not only inhibits collagen hyperplasia to promote tissue repair, decreases the concentration of WBC and fibrin in plasma to reduce tissue inflammation and exudation, but also reduces the permeability of abdominal capillaries and promotes phagocytosis of peritoneal macrophage and microcirculation. Advances in tissue engineering techniques have brought great benefits to the difficult subject of tissue adhesion. Although the application of tissue engineering techniques in tissue adhesion is still in the experimental stage which already presents a very good effect on animals, whether it suits the human body

is still unknown. Therefore, more in-depth research is needed to study wound repaired with tissue engineering materials.

Taken together, the prevention and treatment of tissue adhesion is a problematic situation for surgeons that calls for more study, but fortunately TMP shows unique advantages and certain potential in this field. Pharmacological studies on its activities and clinical application have found TMP's effects on anti-tissue adhesion vary in different concentrations, dosages and administration routes. A safe, effective and reliable biological agent complying with mechanism of adhesive formation will be a direction of the research and development of TMP drug in the future. Meanwhile, new drug delivery system spring up such as grafting effective components of Chinese herbal medicine to magnetic nanoparticles will inspire researchers to optimize the experimental conditions for magnetic nano-drug delivery system of TMP and to perfect its route of administration to prevent abdominal adhesion.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Author Contributions

Yan S designed and wrote the manuscript. Yue YZ helped to write the manuscript. Zong Y participated in the literature selection and Zeng L reviewed and critiqued the manuscript. All authors approved the final version for publication.

REFERENCES

1. Guo M, Liu Y, Shi D. Cardiovascular actions and therapeutic potential of tetramethylpyrazine (active component isolated from *Rhizoma chuanxiong*): roles and mechanisms. Biomed Res Int 2016;2016:2430329.
2. Xu SH, Yin MS, Liu B, Chen ML, He GW, Zhou PP, et al. Tetramethylpyrazine-2'-O-sodium ferulate attenuates blood-brain barrier disruption and brainoedema after cerebral ischemia/reperfusion. Hum Exp Toxicol 2017;36: 670-680.
3. Zhao Y, Liu Y, Chen K. Mechanisms and clinical application of tetramethylpyrazine (an interesting natural compound isolated from *Ligusticum Wallichii*): current status and perspective. Oxid Med Cell Longev 2016;2016:2124638.
4. Gong X, Wang Q, Tang X, Wang Y, Fu D, Lu H, et al. Tetramethylpyrazine prevents contrast-induced nephropathy by inhibiting p38 MAPK and FoxO1 signaling pathways. Am J Nephrol 2013;37:199-207.
5. Wu HJ, Hao J, Wang SQ, Jin BL, Chen XB. Protective effects of ligustrazine on TNF-α-induced endothelial dysfunction. Eur J Pharmacol 2012;674:365-369.
6. Cai X, Chen Z, Pan X, Xia L, Chen P, Yang Y, et al. Inhibition of angiogenesis, fibrosis and thrombosis by tetramethylpyrazine: mechanisms contributing to the SDF-1/CXCR4 axis. PLoS One 2014; 9:e88176.
7. Wang B, Ni Q, Wang X, Lin L. Meta-analysis of the clinical effect of ligustrazine on diabetic nephropathy. Am J Chin Med 2012;40:25-37.
8. Gao C, Liu Y, Ma L, Zhang X, Wang S. Effects of ligustrazine on pulmonary damage in rats following scald injury. Burns 2012;38:743-750.
9. Li KY, Shi CX, Huang JZ, Tang KL. Tetramethylpyrazine effects on the expression of scar-related genes in rabbit benign biliary stricture fibroblasts. J Coll Physic Surg Pak 2016;26:813-817.
10. Chen HY, Xu DP, Tan GL, Cai W, Zhang GX, Cui W, et al. A potent multi-functional neuroprotective derivative of tetramethylpyrazine. J Mol Neurosci 2015;56:977-987.
11. Linderman SW, Gelberman RH, Thomopoulos S, Shen H. Cell and biologic-based treatment of flexor tendon injuries. Oper Tech Orthop 2016;26:206-215.
12. Asmus A, Kim S, Millrose M, Jodkowski J, Ekkernkamp A, Eisenschenk A. Rehabilitation after flexor tendon injuries of the hand. Orthopade 2015;44:786-802.
13. Zhao ZW, Cheng CS, Ma WL, Shan HM, Cheng ZZ, Song GP. Danhong Injection, ligustrazine injection, combined adsorbable biomembranes prevented adhesion of tendons after the repair operation: a clinical research. Chin J Integr Tradit West Med (Chin) 2013;33:1212-1215.
14. Shen L, Du JY, Yang JY, Yang YP, Gao L, Wang L. Experimental and clinical study on ligustrazine Injection in prevention of flexor tendon adhesion. Chin J Integr Tradit West Med (Chin) 1995;15:351-353.
15. Tosun HB, Gümüştaş SA, Kom M, Uludağ A, Serbest S, Eröksüz Y. The effect of sodium hyaluronate plus sodium chondroitin sulfate solution on peritendinous adhesion and tendon healing: an experimental study. Balkan Med J 2016;33:258-266.
16. Rabb CH. Failed back syndrome and epidural fibrosis. Spine J 2010;10:454-455.
17. Wang XY, Li KH, Li X, Hu JZ, Zhang HQ, Liao QD, et al. Clinical study on prevention of epidural adhesion using sodium hyaluronate and ligustrazine after lumbar intervertebral discectomy. Chin J Modern Med (Chin) 2006;16:2026-2028.
18. Gomel V, Koninckx PR. Microsurgical principles and postoperative adhesions: lessons from the past. Fertil Steril 2016;106:1025-1031.

19. Hong G, Vilz TO, Kalff JC, Wehner S. Peritoneal adhesion formation. Chirurg 2015;86:175-180.
20. Diamond MP. Reduction of postoperative adhesion development. Fertil Steril 2016;106:994-997.e1.
21. Schnüriger B, Barmparas G, Branco BC, Lustenberger T, Inaba K, Demetriades D. Prevention of postoperative peritoneal adhesions: a review of the literature. Am J Surg 2011;201:111-121.
22. Wang SH, Mao SH. Clinical efficacy observation of Ligustrazine Injection on adhesive intestinal obstruction. Chin J Surg Integr Tradit West Med (Chin) 2002; 8:275-276.
23. Zhang JY, Liao KS, Wu QF, Luo Z, Liu JL, Yang GQ. Experimental and clinical study of ligustrazine in preventing postoperative intestinal adhesion. J Hubei Instit Natlit (Chin) 2006;23:1-3.
24. Wei L, Zhu FW, Li K, Jiang K, Su QZ. Experimental study of ligustrazine gelatin emulsion on prevention of flexor tendon adhesion. J Guangxi Univ Tradit Chin Med (Chin) 2000;17:57-58.
25. Wang HL. Influence of TMP on adhesion formation during tendon healing. Suzhou: The Fifth Session of the National Youth Sports Science Conference, 2008.
26. Wang HL. Influence of TMP on adhesion formation during tendon healing of collagen. Beijing: The Eighth National Sports Science Conference, 2007.
27. Wei LP, Feng LG, Liu YJ. Application of TTPAM in the prevention of laminectomy epidural adhesions. Jiangxi Med J (Chin) 2013;48:302-305.
28. Chen LK, Xu QX, Meng GC, Li Q, Wu B. Prevention of eperidural fibrosis and adhesion after laminectomy with tetramethylpyrazine and autogenous periosteum graft. Chin J Rehabil Theory Pract (Chin) 2010;16:32-34.
29. Reijnen MM, Bleichrodt RP, van Goor H. Pathophysiology of intra-abdominal adhesion and abscess formation, and the effect of hyaluronan. British J Surg 2003;90:533-541.
30. Reed KL, Fruin AB, Bishop-Bartolomei KK, Gower AC, Nicolaou M, Stucchi AF, et al. Neurokinin-1 receptor and substance P messenger RNA levels increase during intraabdominal adhesion formation. J Surg Res 2002;108:165-172.
31. Fredriksson F, Christofferson RH, Carlsson PO, Lilja HE. Locally increased concentrations of inflammatory cytokines in an experimental intraabdominal adhesion model. J Pediatr Surg 2014;49:1480-1484.
32. Atta HM, Al-Hendy A, El-Rehany MA, Dewerchin M, Abdel Raheim SR, Abdel Ghany H, et al. Adenovirus-mediated overexpression of human tissue plasminogen activator prevents peritoneal adhesion formation/reformation in rats. Surgery 2009;146:12-17.
33. Cassidy MR, Sherburne AC, Sheldon HK, Gainsbury ML, Heydrick S, Stucchi AF. Histone deacetylase inhibitors decrease intra-abdominal adhesions with one intraoperative dose by reducing peritoneal fibrin deposition pathways. Surgery 2014;155:234-244.
34. Karaca T, Gözalan AU, Yoldas O, Bilgin BÇ, Tezer A. Effects of tamoxifen citrate on postoperative intra-abdominal adhesion in a rat model. Int J Surg 2013;11:68-72.
35. Zhang H, Song Y, Li Z, Zhang T, Zeng L, Li W, et al. Evaluation of ligustrazine on the prevention of experimentally induced abdominal adhesions in rats. Int J Surg 2015;21:115-121.
36. Yan S, Yue YZ, Zeng L, Yue J, Li WL, Mao CQ, et al. Effect of intra-abdominal administration of ligustrazine nanoparticles nano spray on postoperative peritoneal adhesion in rat model. J Obstet Gynaecol Res 2015;41:1942-1945.
37. Yan S, Yang L, Yue YZ, Li WL, Zeng L, Yue J, et al. Effect of ligustrazine nanoparticles nano spray on transforming growth factor-β/Smad signal pathway of rat peritoneal mesothelialcells induced by tumor necrosis factor-α. Chin J Integr Med 2016;22:629-634.
38. Xu Y, Pan LQ, Shi Y, Chen DX. Experimental study of peritoneal adhesion in rats after operation using TMP thermo sensitive hydrogels. Jiangsu J Tradit Chin Med (Chin) 2007;39:74-76.
39. Zheng J .The effects of ligustrazine on the formation of peritoneal adhesions and the expression of type Ⅰ or Ⅲ collagens as well as TNF-α or TGF-β1 in rats. Shijiazhuang: Hebei Medical University, 2004.
40. Shi Y. Experimental study of ligustrazine hydrochloride microemulsion on intra-abdominal adhesion. Hunan J Tradit Chin Med (Chin) 2011;27:131-133.
41. Taksaudom N, Ketwong M, Lertprasertsuke N, Kongkaew A. Postoperative pericardial adhesion prevention using collagen membrane in pigs: a pilot study. Open J Cardiovasc Surg 2017;9:1179065217720909.
42. Sri D. Is cardiac surgery getting more complicated? Indian J Thorac Cardiovasc Surg 2012;28:275.
43. Colak N, Nazli Y, Alpay MF, Aksoy ON, Akkaya IO, Bayrak R, et al. Effect of topical N-acetylcysteine in the prevention of postoperative pericardial adhesion formation in a rabbit model. Cardiovasc Pathol 2013;22:368-372.
44. Han LH, Chen T, Feng GQ. Protective effects of ligustrazine and sodium hyaluronate and contrast study on rabbit's postoperative pericardial adhesion. Chin J Clin Pharmacol Ther (Chin) 2006;11:665-668.
45. Shi DZ. Research progression in the pharmacological of ligustrazine. Chin J Integr Tradit West Med (Chin) 2003;23:377-378.

(Accepted May 3, 2018; First Online January 9, 2019)
Edited by TIAN Lin