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Acupuncture and Biliary Function Regulation: A Mini-Review

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1. Abstract

Biliary Dyskinesia (BD) is considered to be an important factor in the development of various biliary system diseases, and acupuncture has been shown to be effective in the treatment of BD. However, due to the lack of systematic and comprehensive review articles, the efficacy and potential mechanisms of clinical treatment for treating BD have not been clarified. Therefore, the purpose of this review is to discuss the efficacy of acupuncture as a therapy for BD and the associated potential mechanisms. In this review, we systematically discussed the improvement of clinical symptoms of BD after the treatment of acupuncture, discussed the modulation of BD by acupuncture in terms of gallbladder wall thickness, gallbladder contractive function, and Oddi's contractive function, and summarized the literature on acupuncture treatment of BD. Our results suggest that the role and more systematic mechanism of acupuncture for BD needs to be further investigated in order to provide creative ideas for future research, and practical significance for clinical guideline. Acupuncture treatment for BD is worth promoting and hopefully will benefit more patients.

2. Introduction

Biliary Dyskinesia (BD) is a functional gastrointestinal disorder, also known as "biliary dysfunction"or "Acalculous cholecystitis",including Gallbladder Dyskinesia (GD) and Sphincter of Oddi Dysfunction (SOD) [1, 2]. The main symptoms of BD are moderate to severe epigastric and right upper quadrant abdominal pain, which can radiate to the right shoulder or even to the lower back. The pain caused by BD usually lasts around 30 minutes and is accompanied by bloating, indigestion, and nausea [3]. But repeated examinations did not reveal any anatomical obstruction, such as gallstones or common bile duct stricture [4]. The incidence of BD was reported to have increased significantly over the decade, from 43.3 to 89.1 cases per 1 million people [5]. Between 1997 and 2010, it is tripled of that number of patients hospitalized with BD as the primary diagnosis. The increase was even more pronounced for children [6] (700% increased). As medical technology and basic research progress, A growing body of evidences indicate that BD may be an important factor that induces biliary diseases [7]. Gallbladder motility and/or sphincter of Oddi dysfunction can evolve into organic lesions. BD is not only the pathogenesis of most biliary and pancreatic inflammatory and functional diseases, but also a key secondary pathological change in these disorders, seriously affecting the quality of life [8-10].

Cholecystectomy is now known as one of the treatments for BD. Cholecystectomy is less reliable in relieving BD symptoms than in cholelithiasis, especially in the case of a typical symptoms, and only 50% of stone-free patients are reported to be pain-free after cholecystectomy [11]. This is another important factor that must be included in the risk-benefit ratio. Therefore, patients should not undergo cholecystectomy aggressively [12-14]. In order to mitigate excessive surgery, it is necessary to find an effective and low-risk method for treating biliary tract disorders. Therefore, research on the efficacy of acupuncture in the treatment of biliary tract diseases and its related mechanisms has received increasing attention.

Acupuncture has a history of more than 3,000 years and is an indispensable part of the history of traditional Chinese medicine [15].

Acupuncture is guided by the theory of traditional Chinese medicine,the needle (usually refers to the filiform needle) is inserted into the patient's body at certain angle to stimulate specific parts of the body to treat diseases. It has been widely used in clinical practice [16]. Acupuncture treatments include Manual Acupuncture (MA), Electroacupuncture (EA), and Transcutaneous Electric Nerve Stimulation (TENS), MA refers to the manipulation of the inserted needles by hand, such as lifting and inserting, twisting, or other complex combinations [17]. EA is a modification of the traditional acupuncture and involves inserting acupuncture points and pass (sense) the micro current wave of human bioelectricity on the needle [18]. TENS is a therapeutic application of transcutaneous (over the skin) electrical stimulation, usually using adhesive electrodes applied to the skin surface to apply pulsed electrical stimulation [19]. Acupuncture, one of the most popular alternative and complementary therapeutic measures used in Traditional Chinese Medicine (TCM) [20], it has been shown to be an effective and safe treatment for BD, not only in relieving painful symptoms of BD, but also in nausea, vomiting and gastrointestinal function, and even in relieving patients of biliary colic secondary to the formation of gallstones [21-25].

Hence, this mini-review provides a comprehensive summary of the modalities and approaches for BD by acupuncture.

3. Acupuncture Relieves BD Symptoms

Acupuncture has been proven to relieve patients' pain and improve associated gastrointestinal symptoms, with the advantage of being able to apply to pregnant patients as well [26, 27]. A study showed that MA at GB21 not only relieved the patient's right upper quadrant pain, but its involvement of the back shoulder pain [28]. It is known that when gallbladder contractile dyskinesia occurs, its afferent impulses travel through the right phrenic nerve to segments 3-5 of the cervical segments of the spinal cord, which belongs to the same segment as the distribution of the cutaneous nerve in the right shoulder, thus causing right shoulder referred pain. GB21 is the only meridian point of the foot Shaoyang gallbladder meridian traveling to the back of the shoulder, and MA at GB21 can reflexively modulate visceral functions via this pathway, from which may benefit for relieving gallbladder pain [29]. In another clinical study, acupuncture at LR3, GB34 and ST25 has been shown to be effective in relieving pain caused by SOD and reducing the frequency and severity of pain episodes [30]. The reason for choosing LR3is because in TCM theory, "the liver and gallbladder are in perfect sympathy with each other", LR3 is the Yuan point and Shu point of the Foot JueYin Liver Meridian, biliary disease causes; GB34 is a He point of the Foot Shaoyang Gall Bladder Meridian, which is mainly used to treat biliary diseases. Clinical studies have also confirmed that toning liver meridian points can help with biliary system disorders [31]. According to TCM theory, "The spleen and stomach are the origin of acquired constitution, so strengthening of the spleen and stomach can support the righteousness and drive away the evil, so in the treatment of BD, ST25, the point of Foot Yangming Stomach Meridian is chosen [31]. In addition, acupuncture can be used not only as a stand-alone treatment option for BD, but its combined herbal treatment for chronic cholecystitis is significantly more effective than oral herbal medicine alone [32].

4. Acupuncture and Gallbladder Dyskinesia Regulation

Gallbladder dyskinesia is a group of syndromes resulting from primary or metabolic disorder of the tension of gallbladder, which can lead to impaired gallbladder emptying [2, 33].

4.1. Acupuncture for the Reduction of Gallbladder Wall Thickness

Thickening of Gallbladder wall is regarded as one of the causes of gallbladder dyskinesia [34]. The inflammatory response is the main cause of gallbladder wall thickening [35]. Acupuncture can significantly regulate cytokines released from abnormally activated macrophages by balancing the M1/M2 macrophage ratio and modulating cytokine levels in the inflammatory environment [36], or it can dynamically regulate various inflammatory factors, including interleukins (IL) [37], Tumor Necrosis Factor (TNF) [38, 39], Interferon (IFN) [40], etc. In rabbits with acute cholecystitis, EA at GB34 and SP9 can reduce the inflammatory response, which in turn improves the congestion and edema of the gallbladder mucosa and promotes the absorption of fibrin exudates from the plasma membrane, ultimately acting to repair the gallbladder wall and reduce its thickness. Among them, the GB34 point is more effective than the SP9 point [41]. In another research, it has been demonstrated that EA at GB34, ST37, ST39, and ST36 points can produce different degrees of therapeutic effects on guinea pigs with acute cholecystitis, probably due to the inhibition of inflammatory factors and reduction of inflammatory response by regulating the expression of TNF-α and nAchR α7 mRNA; the intervention effect of the GB34 group was more prominent than that of the other acupuncture points, indicating the relative specificity of the GB34 acupuncture point for BD treatment [42]. It further proves the idea of Treatment with syndrome differentiation in TCM.

4.2. Acupuncture Regulates the Contractile Function of the Gallbladder

Three methods including ultrasound examination, MRI and Cholecystokinin–Cholescintigraphy [4] were used to measure BD. Ultrasound examination is the most common test [43], and it is able to evaluate the systolic and diastolic function of the gallbladder by measuring fasting and postprandial gallbladder volume changes [44].

Table 1: The effects of acupuncture on BD

Region	Method	Results	Ref.
GB21	MA	Relief of right upper quadrant abdominal pain; Relief of shoulder and back pain	28
GB21	MA	↑ or ↓ the volume of the gallbladder	29
GB34	EA EA EA EA/MA EA/MA EA	Relief pain caused by SOD; Reduce the inflammatory response; Inhibition of inflammatory factors; ↑gallbladder contraction; ↑VIP,↓SO electromyography; Relax SOD	30 41 42 45 51 45 63 64
GB24	EA	↑cck &VIP secretion	62
SP9	EA	reduce the inflammatory response;n	41
LR3	EA	Relief pain caused by SOD	30
LR14	EA/MA EA/MA EA	↓gallbladder contraction ↑SO electromyography ↑cck \VIP secretion	45 45 54 62
LI4	TENS	↓SO pressure	61
ST25	EA EA	Relief pain caused by SOD; ↓gallbladder contraction; ↑SO electromyography	30 45 45 54
CO11	EA	↑gallbladder contraction ↓SO electromyography	45 45
ST36	EA	Inhibition of inflammatory factors	42
ST37	EA	Inhibition of inflammatory factors	42
ST39	EA	Inhibition of inflammatory factors	42

↑,increase; ↓, decrease. EA: Electroacupuncture; MA: Manual acupuncture; GB21: jianjing; GB34: yanglingquan; GB24: riyue; LR14: qimen; SP9: yinlingquan; LR3: taichong; ST25: tianshu; ST36: zusanli; ST37: shangjuxu; ST39: xiajuxu; LI4: hegu; ST25: tianshu; CO11: yidan

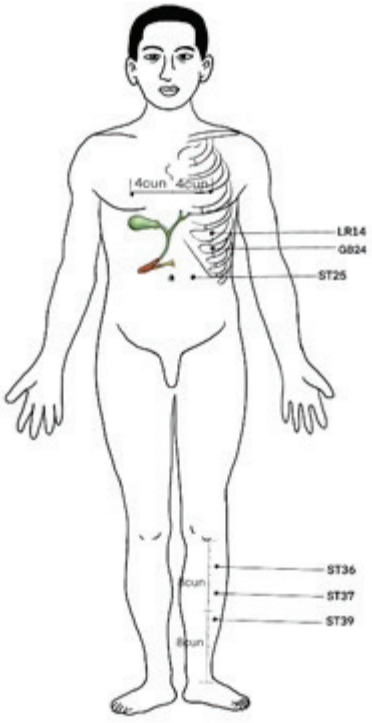

Figure 1: Gallbladder,sphincter of Oddi,Location of acupoints often used in Biliary dyskinesia

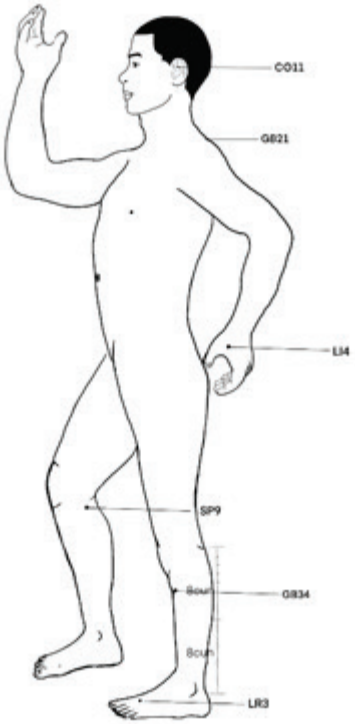

Figure 2: Location of acupoints often used in Biliary dyskinesia

4.2.1. Acupuncture modulates nerve regulation of gallbladder contraction

Especially, the magic effect of acupuncture is that it has a dual-direction regulatory effect. An experimental study showed that gallbladder pressure decreased with either MA or EA at ST25 and LR14. In contrast, MA or EA at GB34 and CO11 resulted in an increase in gallbladder pressure. The dual-directional effect of acupuncture on the extrahepatic biliary system was confirmed. The mechanism is related to sympathetic/parasympathetic modulation [45].

4.2.2. Acupuncture regulates gastrointestinal hormones of gallbladder contraction

The function of the gallbladder and the Oddi sphincter is regulated by hormones produced in the gastrointestinal tract [46]. Cholecystokinin (CCK) plays an important role in gallbladder contraction [47]. CCK is secreted by I cells within the proximal small bowel. CCK is widely distributed and is not only found in the duodenum and jejunum, but also found in neurons in the distal ileum, colon, and brain. It controls the contraction and emptying of the gallbladder

and the release of pancreatic enzymes. Downregulation of cholecystokinin receptor mRNA expression leads to reduced sensitivity of the gallbladder to cholecystokinin, which in turn causes a decrease in gallbladder contractile function [33, 48, 49]. Acupuncture has been shown to have effects on enhancing the cholecystokinin level [50]. In patients with chronic cholecystitis, EA at GB34 causes contraction of the gallbladder smooth muscle and induces gallbladder emptying. While the gallbladder smooth muscle contracts, the gallbladder artery is squeezed by the gallbladder smooth muscle, and the blood flow velocity decreases and the resistance index. It is suggested that EA at GB34 could promote the secretion of cholecystokinin in patients with chronic cholecystitis, improve and restore the contractile function of the gallbladder, which promote gallbladder emptying to achieve the therapeutic purpose [51, 52].

5. Acupuncture for Regulation of SOD (Sphincter of Oddi Dysfunction)

The sphincter of Oddi is kind of smooth muscle valve regulating the flow of biliary and pancreatic secretions into the duodenum, SOD refers to a variety of biliary, pancreatic and hepatic disorders caused by spasm, stenosis and relaxation of the valves at inappropriate times [53]. Motor function disorders and stenosis are the development, evolution of SOD from mild to severe stage.

5.1. Acupuncture for Neuro-Modulation of SOD

According to TCM, one characteristic of acupuncture is that it has different regulatory effects during different acupuncture point stimulation. For instance, MA or EA at ST25 or LR14 significantly increased the frequency and amplitude of SO electromyographic activity; In contrast, MA or EA at GB34 or CO11 significantly decreased SO electromyography [45], which further confirmed this dual-directional effect of acupuncture on the biliary system. And this interesting paradox is considered to be related to sympathetic/parasympathetic nervous regulation of acupuncture, which is consistent with the viewpoint of TCM. The same series of experiments also found that EA at LR14 and ST25 in guinea pigs relatively promoted the myoelectricity of SO and reduced the bile flow into the duodenum, while acupuncture at GB34 relatively promoted the contraction of the gallbladder and inhibited the myoelectricity of the oddi sphincter. The effect of GB34 was significantly higher than that of other acupuncture points [54].

5.2. Acupuncture Regulates SOD Through Body Fluids

There are growing evidence that control of SO motility involves complex interactions between nerves, neurotransmitters, and gastrointestinal hormones such as Vasoactive Intestinal Peptide (VIP) and CCK[55-58]. Changes in VIP and CCK may be an important cause of SO dysfunction [59]. VIP is an inhibitory neurotransmitter in the gastrointestinal tract, and VIP nerves are found in abundance in the SO, pyloric sphincter, and lower esophageal sphincter [60]. From clinical human studies, TENS of the LI4 acupuncture point for 45 min resulted in an increase in VIP in serum and a decrease in SO pressure [61]. And in an animal experiment, it was shown that CCK cells were more and significantly distributed in the duodenum, gallbladder and SO after electroacupuncture LR14 and GB24. However, VIP cells were significantly different in number in duodenum and SO, but not in the gallbladder. So in conclusion that EA regulates biliary motility by increasing the distribution of CCK and VIP containing cells in the duodenum and SO [62]. A Korean study showed that the effect of the GB34 acupoint on SO movement was sensitive and specific compared to GB34 at a distance of 5 cm. During EA at GB34, significant reductions in all parameters of SO motility were associated with elevated CCK levels in plasma. Furthermore, after cessation of EA stimulation, SO contractility returned almost to basal levels and was accompanied by a recovery of CCK plasma levels. The close relationship between CCK plasma levels and SO contractility suggests that increased levels of CCK in circulation may be responsible for the inhibition of SO contraction during electroacupuncture stimulation. Importantly, the inhibition of SO contractility by electroacupuncture preceded the increase in CCK plasma levels. In addition, CCK plasma levels did not change significantly within 2.5 min and only increased significantly 5 min after electroacupuncture stimulation, suggesting that the effect of EA on SO movement may due to multiple mechanisms of neural and hormonal interactions, rather than just the action of CCK [63, 64]. Interestingly, several groups of experiments overlapped in the choice of acupuncture points but had different effects on the function of SO, and this is where the magic effect of acupuncture lies. Needling one point or needling several different points at the same time can have different effects on the body. In general, experiments have shown that EA can relieve the sphincter of Oddi dysfunction. Due to TCM believes that SO is related to biliary disease, so effective points are often taken to treat biliary disease in experiments, also known as treatment with syndrome differentation.

6. Conclusion

Although acupuncture has been used as an appropriate adjuvant treatment for biliary tract dysfunction disorders, the underlying mechanisms are not clearly understood. There are no systematic and comprehensive review articles elucidating the modulatory effects of acupuncture on biliary tract function. In this review, we discussed the improvement of discomfort symptoms of BD by acupuncture, including pain and gastrointestinal reactions, and also discussed the modulation of BD by acupuncture in terms of gallbladder wall thickness, gallbladder contractile function, and function of SO. In addition, acupuncture can dual-directionally regulate the diastole and systole of the gallbladder and SO. According to classical acupuncture theory, acupuncture points are important reflex points for visceral dysfunction. Different acupuncture points have different therapeutic effects.GB34, GB21, SP9, ST36 are the main acupuncture points for treating patients or animals with biliary tract diseases, indicating the specificity of acupuncture points. The duration and frequency of acupuncture manipulation are important parameters for the success of

acupuncture treatment. Therefore, future studies should incorporate the selection of acupoints and stimulation parameters to optimize the method. Explaining the magic effect of TCM charms with scientific results. The mechanisms of beneficial effects of acupuncture may be related to neurological pathways and transmission. However, the neural pathways through which acupuncture modulates biliary dysfunction have not been identified. The stimulation time and amplitude of acupuncture for BD has not been mentioned in the literature, and future studies should refine the distinction between MA and EA stimulation time. Although both EA and MA are effective in modulating biliary tract disorders, it is unclear which is more effective in some cases. Further studies on the efficacy of acupuncture on multiple targets may be more likely to trigger scientific interests. In addition, more basic experimental studies are required in future research to elucidate the signaling pathways of the biliary tract regulated by acupuncture and provide new therapeutic approaches for the treatment of various biliary tract diseases.

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