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EDITORIAL

Anesthesia and acupuncture

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Abstract

Using acupuncture instead of anesthetics to induce analgesia was performed in China many years ago in surgical anesthetization. Although many medical units in China's cities and rural areas are applying these techniques in operations, it should be pointed out that acupuncture anesthesia is still in the process of development and is of next to no practical and even less scientific value in the western world. However, acupuncture-assisted anesthesia can be useful also in countries other than China.

Key words: Anesthesia; Acupuncture; Anesthesiology; Acupuncture-assisted-anesthesia; Sedation

Core tip: Acupuncture anesthesia has been converted into acupuncture-assisted anesthesia in China. Acupuncture-assisted anesthesia reduces the demands of anesthetics and the post-operative complications and has a potential organ protective effect.

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INTRODUCTION

Using acupuncture instead of anesthetics to induce analgesia was performed in China many years ago in surgical anesthetization. Although many medical units in China's cities and rural areas are applying these techniques in operations, it should be pointed out that acupuncture anesthesia is still in the process of development and is of next to no practical and even less scientific value in the western world[1]. However, acupuncture-assisted anesthesia can be useful also in countries other than China.

The objective of this editorial is to present the

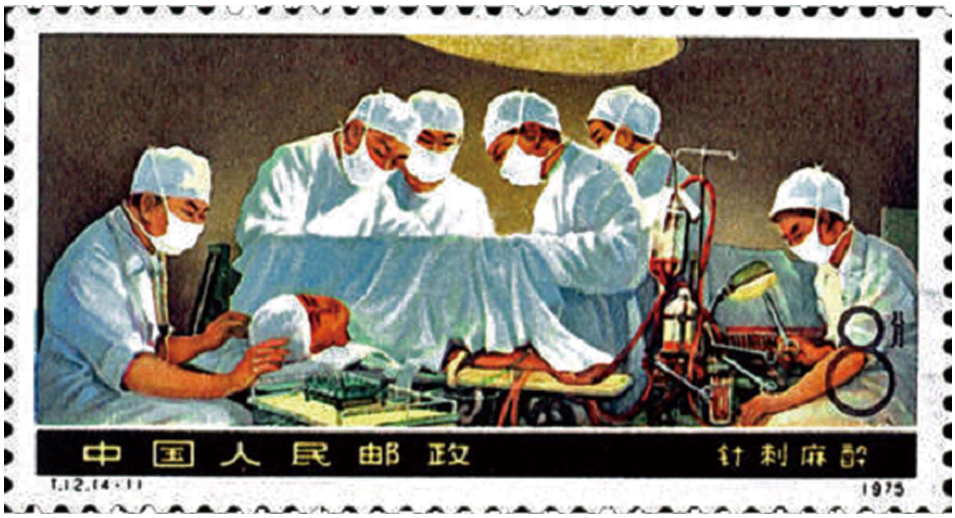

Figure 1 "Acupuncture anesthesia" stamp.

experience with acupuncture-assisted anesthesia that can be found in the scientific literature. Showing traditional approaches to anesthesia may help to tackle problems that are still evident, such as postoperative nausea and pain. Evolution is usually a combination of conservatism and innovative thinking. The editorial should provide an open-minded account of experiences with acupuncture-assisted anesthesia, balanced with skepticism.

FIRST REPORTS ON EVIDENCE AND PERSPECTIVE

For many thousands of years, acupuncture has been proven effective in relieving pain[2]. Acupuncture anesthesia developed from acupuncture analgesia[2].

Two of the first reports concerning acupuncture-assisted anesthesia came from the Shanghai First People's Hospital dated August 30 and September 5, 1958[2,3]. Doctors of Chinese and Western medicine worked together and learned from each other. Dr. Yin Huizhu carried out a tonsillectomy with acupuncture anesthesia without further use of anesthetics[2,3]. In the same year, electroacupuncture anesthesia was used for the first time at the 4th People's Hospital of Xi'an[3]. A pneumonectomy under acupuncture anesthesia was performed in 1960 at the First Tuberculosis Hospital of Shanghai[2]. After this event, many satisfactory results were also obtained in other operations (cardiac surgery, total laryngectomy, cesarean section, surgery on the anterior cranial fossa, *etc.*)[2]. In 1971, Xinhua News reported about acupuncture anesthesia. The headline was "The Chinese medical personnel and scientists successfully invented acupuncture anesthesia", and it was stated that more than 400000 surgical patients had undergone acupuncture anesthesia[3]. On July 26, 1971, even the New York Times published one of the first articles - "Now, let me tell you about my appendectomy in Peking …" - in the Western world on acupuncture anesthesia. Richard Nixon was the first United States President to visit China. At about that time, acupuncture started to become known to people outside Asia. As a consequence, in March 1972, Professor Johannes Bischko from Austria was the first surgeon in the West to perform a tonsillectomy with only acupuncture analgesia[4]. In 1975, as a sign of special recognition, a memorial stamp for the invention of acupuncture anesthesia was issued in China. The stamp shows a scene from the operating theater, and below it is written "acupuncture anesthesia"[5] (Figure 1).

By 1980, many surgeries had been performed under acupuncture anesthesia[2]. From 1986 to 2000, three Chinese national key projects were carried out, supported by the Chinese central government. Famous hospitals, *e.g.,* from Beijing, Shanghai and Chengdu, participated in these studies. In these years, acupuncture mainly played a cooperating role in combination with drugs. Therefore, acupuncture combined with selected drugs was named "acupuncture-drug balanced anesthesia" or "acupuncture-balanced anesthesia"[2]. Because of several reforms in China and the import of modern anesthetic technology, acupuncture-induced anesthesia began to be deemed inadequate. Meanwhile, in China the term "acupuncture anesthesia" has been replaced by "acupuncture-assisted anesthesia" (similar to "acupuncture-balanced anesthesia"). The main goal of this "acupuncture-assisted anesthesia" is the reduction of the dosage of anesthetics, a reduction of the related complications and the protection of the involved organs like brain and heart.

In a documentary from 2006, which is part of a BBC series hosted by Kathy Sykes and has been released on the internet[6], a patient in China is having open heart surgery without general anesthesia, but with acupuncture "instead" (Figure 2). However, the report is massively biased to exaggerate the role of acupuncture. It is casually mentioned that the patient

Figure 2 The photos show cardiac surgery under acupuncture-drug balanced anesthesia at the Renji Hospital, Shanghai[6].

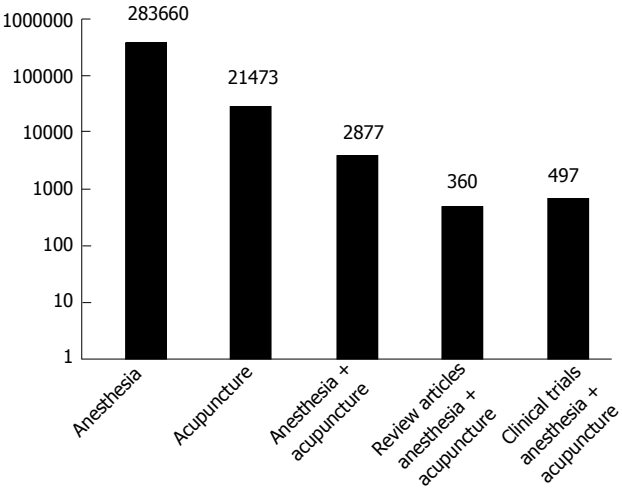

Figure 3 Scientific database research.

had undergone sedation and local anesthesia (her chest was numbed), as if this was a tiny detail[7]. There is no mention of whether or not you could have the same procedure with conscious sedation and local anesthesia, but without the acupuncture[6,7].

The scene in the BBC documentary[6,8] which shows the 21-year-old patient undergoing heart surgery punctured with needles left viewers under the strong impression that acupuncture was providing immense pain relief. However, Singh reported in "The Telegraph"[9] that "in addition to acupuncture, the patient had a combination of three very powerful sedatives (midazolam, droperidol, fentanyl) and large volumes of local anaesthetic injected into the chest"[9].

Although acupuncture-assisted anesthesia for open heart surgery has declined in recent years, there is a renewed interest in it due to the escalating medical costs. Zhou *et al*[10], for example, came to the conclusion that a combined acupuncture-medicine anesthesia strategy can reduce the postoperative morbidity and medical costs in patients undergoing open heart surgery under cardiopulmonary bypass[10].

It is the authors' opinion that acupuncture-anesthesia alone will never be used in the western world, since modern technology offers better and safer possibilities. However, acupuncture does represent a very good method to alleviate the side-effects of anesthesia such as post-operative nausea and vomiting, pain and dizziness, which has been shown in several studies[1,11-13].

A literature research in the scientific database PubMed (Oct 31, 2014) shows many studies concerning the topic "anesthesia and acupuncture"; there are also almost 500 clinical trials on this topic (Figure 3). Several review articles, *e.g.*, the paper by Lee *et al*[14] in *Pain*, concluded that "This review does not support the use of acupuncture as an adjunct to standard anesthetic procedures during surgery"[14].

CONCLUSION

Acupuncture anesthesia has been converted into acupuncture-assisted anesthesia in China. Acupuncture-assisted anesthesia reduces the demands of anesthetics and the post-operative complications and has a potential organ protective effect. Therefore, acupuncture may be an excellent adjunct to reduce peri- and postoperative pain. This conclusion, however, has to be explored in detail in further scientific studies.

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EDITORIAL

Benzodiazepine in spinally mediated analgesia

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Abstract

Since benzodiazepine/γ-amino butyric acid receptor was found in the spinal cord, there have been many studies to investigate analgesic effects of midazolam, a water-soluble benzodiazepine in the spinal cord. In animal experiments, intrathecal midazolam has analgesic effects on visceral pain, thermal pain, and inflammatory pain, and it has synergistic or additive effects with different kinds of analgesics acting on different receptors. In human study, intrathecal midazolam has analgesic effects on back pain, somatic pain, but not visceral pain. The analgesic effect lasts long and intrathecal midazolam induces sedation, which is the effect in the brain. Epidural midazolam is less studied than intrathecal midazolam. Epidural midazolam has segmental analgesia for postoperative pain, and adding midazolam to bupivacaine increased duration of analgesia. It also induces sedation, which might be the effects of midazolam coming from cerebrospinal fluid to the brain. Some histopathological studies in animals showed neurotoxicity of midazolam, while there are no toxic side effects in many human studies of intrathecal and epidural midazolam. Therefore, we need clinically relevant animal studies for neurotoxicity and analysis of complications in patients already studied with intrathecal and epidural midazolam to give final conclusion.

Key words: Spinal cord; Analgesia; Benzodiazepine; Neurotoxicity; Intrathecal; Epidural

Core tip: Intrathecal or epidural midazolam has analgesic effect acting on benzodiazepine/γ-amino butyric acid receptor in the spinal cord. Many clinical and animal studies showed no harmful side effects, while in some animal experiments, neurotoxicity was found. Therefore, we need further evidence to bring it into clinical application.

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INTRODUCTION

The first spinal analgesia was done in 1898 by August Bier using cocaine[1]. Since then many local anesthetics has been used for spinal anesthesia without neurotoxicity studies. Recent decades, morphine, hydromorphone, fentanyl and sufentanil are also administered intrathecally with a few neurotoxicity studies, too. Intrathecal opioids induce many side

effects; respiratory depression, nausea, vomiting, sedation, pruritis, constipation, urinary retention, cognitive impairment, and headache. Therefore, to avoid these side effects, other agents such as baclofen, clonidine, etc. for intrathecal use have been enthusiastically investigated.

The benzodiazepine/γ-amino butyric acid (GABA)$_A$ receptor coupling in the spinal cord has a great role in analgesic mechanisms[2]. Therefore, since 1980's, many clinical and animal studies have been performed to investigate analgesic effects of intrathecal midazolam, a water-soluble benzodiazepine[3,4] as substitution for opioids. However, clinically intrathecal midazolam is not widely used because some animal experiments showed neurotoxic results[5-7]. The review by Yaksh *et al*[8] pointed that intrathecal midazolam is neurotoxic, therefore, it should not be used in human, while some animas studies showed no neurotoxicity.

Now United States Food and Drug Administration (FDA) approves only morphine, ziconotide, and baclofen for human intrathecal use. However, no neurotoxicity studies were found for ziconotide and only a few have been performed for baclofen and morphine. Therefore, the reason of the FDA approval for only these three agents, and why the review by Yaksh *et al*[8] targeted only midazolam and did not deny using other agents intrathecally are not clear.

This article summarizes clinical and experimental evidences of spinally mediated analgesia by benzodiazepines, especially midazolam.

ANALGESIC MECHANISMS

GABAergic neurons and GABA$_A$ receptors exist in the spinal cord dorsal horn and they inhibit the conductance of pain signals from periphery to central nervous system. The decrease of this inhibition induces pain[9]. The analgesic effects of benzodiazepines are mainly mediated *via* benzodiazepine/GABA$_A$ receptors in the spinal cord[10,11]. Midazolam decreases excitatory synaptic transmission at the benzodiazepine/GABA$_A$ receptor in interneuron, then decreases excitability of spinal dorsal horn neurons[12], and increases duration and amplitude of GABAergic synaptic current by acting on the benzodiazepine/GABA$_A$ receptor in substantia gelatinosa neurons[13]. Thus, intrathecal midazolam induces segmental analgesia[11]. Midazolam also acts on δ receptors in the spinal cord to release endogenous opioid[14], and directly acts as an agonist at κ opioid receptors[15], but does not have a local anesthetic action[4].

BASIC RESEARCH

In 1987, Goodchild *et al*[4] showed that intrathecal midazolam had analgesic effects in rat, and in 1993, analgesic effects of intrathecal midazolam on visceral pain in rabbits were reported by Crawford *et al*[16]. Another benzodiazepine, chlordiazepoxide has also spinally mediated analgesic effects[17].

Many studies have shown interaction between intrathecal midazolam and other agents acting on different receptors. In the isolated neonatal rat spinal cord, midazolam and alfentanil had synergistic depression of nociceptive neurotransmission[18]. Intrathecal midazolam potentiated analgesic effects of intrathecal morphine, but intracerebroventricular midazolam inhibits analgesia by intracerebroventricular morphine, which are mediated by GABA$_A$ receptors in the spinal cord and brain, respectively[19]. Intraperitoneally administered midazolam had analgesic effect on inflammatory acute and facilitated pain, but not on acute thermal pain, while intrathecal midazolam had analgesic effects on both thermal and inflammatory pain in rat[20]. The 50% effective dose for thermal pain was higher than that for inflammatory pain, therefore, the dose of intraperitoneal midazolam used in this study was not enough dose to have spinally mediated analgesia for thermal pain. Intrathecally administered midazolam has synergistic or additive analgesic effects with N-methyl-D-aspartate receptor antagonist, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist[21,22], clonidine, α2-adrenergic receptor agonist[23], bupivacaine[24], and serotonin[25] on thermal and inflammatory pain in rat. However, intrathecal midazolam and nicotinic cholinergic agonist had antagonistic effects on thermal acute pain, while they have synergistic or additive effects on inflammatory pain[26]. From these animal studies, intrathecal midazolam is effective analgesic.

NEUROTOXICITY

Before clinical application of intrathecal agents, neurotoxicity must be investigated. However, many spinally or epidurally administered agents; lidocaine, morphine, etc. in human have not been studied enough for their neurotoxicity. Lidocaine is neurotoxic at high concentrations[27], and even at clinical concentrations it changed neurophysiology[28]. In spinal anesthesia, lidocaine induced abnormal neurological symptoms[29]. No histological changes were reported with epidural morphine[30,31], while inflammatory response and fat cell necrosis by epidural morphine were reported[32]. Morphine also induces apoptosis in the brain and spinal cord[33], and neuron death[34]. Fentanyl is absent from neurotoxicity studies. Even natural peptides and amino acids are neurotoxic when administered at high concentration[35].

Some animal studies observed neurotoxicity of intrathecal midazolam[36-40]. Werdehausen *et al*[41] showed that adding midazolam to lidocaine increased neuronal cell death by additive induction of mitochondrial apoptosis. However, other animal studies showed no neurotoxicity of intrathecal midazolam[5-7]. Even a continuous intrathecal infusion of midazolam for 43 d in sheep and pigs showed no histopathological changes in the spinal cord[6]. Many of these studies used

intrathecal catheter, which itself might induce some histopathological changes in the spinal cord. The direct administration of midazolam 10 mg on the cat spinal cord, which dose is quite higher than clinical doses, did not induce any histopathological changes including inflammatory changes[42]. This study did not use any catheters, therefore, it excluded the influence of physical changes. However, observation period in this study was only 6 h after administration. The acidic pH of midazolam might have some damage to the spinal cord, but midazolam administered intrathecally does not decrease pH of cerebrospinal fluid less than 7[43]. Therefore, acidity of midazolam could be neglected.

Neurological symptoms did not increase with intrathecal midazolam in human study by Ho *et al*[44]. The cohort study of safety of intrathecal midazolam investigating 1100 patients showed no neurological and urologic adverse symptoms by intrathecal midazolam[45], and many other clinical studies cited below showed no irreversible adverse effects. Therefore, discussion about neurotoxicity of midazolam did not finish yet until large clinically mimetic animal neurotoxicity studies. In addition, follow up of the patients received intrathecal or epidural midazolam is necessary.

CLINICAL STUDIES

Spinal administration

Intrathecal midazolam has analgesic effects on chronic back pain[46,47] and somatic pain, but not visceral pain[3]. The effect of intrathecal midazolam was segmental and had no effects on sympathetic tone and reflexes[48]. The duration of analgesia by intrathecal midazolam was less than 6 h, which became longer than 6 h by adding diamorphine[49]. Prochazka *et al*[47] showed that analgesic effects on chronic low back pain lasted 9.7 wk, while in 13% no analgesia was obtained. The duration of sensory block by intrathecal midazolam lasted for 72 h in the study by Goodchild *et al*[3]. Many studies showed that adding intrathecal midazolam to bupivacaine increased duration of analgesia[48-55]. Only one study showed no change in the duration of analgesia by adding intrathecal midazolam to bupivacaine, while duration of motor block lasted longer without changing the duration of sensory block[56]. Yegin *et al*[53] reported that the onset and recovery from sensory and motor blocks were not altered, while Wu *et al*[57] showed fastened recovery of motor function. Therefore, intrathecal midazolam might increase duration of analgesia by bupivacaine, but duration of motor and sensory block might not always increase. Intrathecal midazolam induced sedation[53,58] and decreased nausea and vomit[44,54,58], which are the effects in the brain not in the spinal cord, and they are advantages for pain management.

Epidural administration

In comparison with intrathecal midazolam, only a few studies have been performed for epidural midazolam. The first report of epidural benzodiazepine was by Lin *et al*[59], which showed that epidurally administered diazepam by mistake induced reversible motor and sensory block and analgesia.

Epidural midazolam induced wide range of analgesic dermatomes[60-64], and fastened onset of sensory block and time to peak effect, and prolonged duration of motor and sensory blocks of epidural lidocaine[65]. Continuous epidural administration with bupivacaine, midazolam increased analgesic effect[66-68]. This combination potentiated analgesic effect of epidural morphine, but inhibited that of fentanyl[69]. This different effect with morphine and fentanyl might be due to their different lipophilicity. Midazolam antagonized the effect of fentanyl in the brain, but potentiated the effect of morphine in the spinal cord.

Epidural midazolam induced sedation, but serum concentration of midazolam was less than that induces sedation. Therefore, midazolam went into the brain by cerebrospinal fluid[70]. However, in an animal study, after epidural administration of midazolam, concentration of midazolam in cerebrospinal fluid was only 3% of that in serum[71], while it might be enough concentration to induce sedation in the brain.

CONCLUSION

Intrathecally or epidurally administered midazolam has analgesic effect by acting on the benzodiazepine/$GABA_A$ receptor in the spinal cord. It induces sedation and decreases nausea and vomit, which are the advantage induced by the action in the brain. Neurotoxicity of midazolam is still controversial, while no clinical neurotoxicity was found. Therefore, further clinically mimetic animal neurotoxicity study is necessary.

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