



Are Acupuncture and Acupressure effective in decreasing chemotherapy-induced nausea and vomiting in children?

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Abstract

Acupuncture and acupressure are some of the most common non-pharmacological treatment modalities in the world, with evidence suggesting they may be useful in treating chronic diseases. There is a growing body of literature that suggests that acuthery is effective in treating chemotherapy-induced nausea and vomiting (CINV) in adults, but few trials and reviews have been conducted on the effect of acuthery in children. Thus, the primary objective of this review was to provide a robust and comprehensive summary of the existing literature on the efficacy of acupuncture and acupressure to treat CINV, with a specific focus on youth aged five to eighteen years. The secondary objective was to evaluate how the acupoints' anatomical and physiological nerve connections affect nausea and vomiting reflexes. The most effective acupoints reported were Pericardium 6 (PC-6), Large Intestines 4 (LI-4), and Stomach 36 (ST-36). Acupuncture at ST-36 and PC-6 was suggested to stimulate the vagus nerve, vestibular system, and/or modulate neurotransmitters to help control nausea and vomiting. Future research should increase clinical trial cohorts to detect statistically significant differences if they exist, focus on specific acupoints to determine the efficacy of each point, and explore the impact of the placebo effect on sham acupuncture. A double blinded clinical trial design was proposed in this paper to address this long standing conundrum about the placebo effect in acupuncture procedures.

Keywords

Acupuncture, Acupressure, Acuthery, Chemotherapy-Induced Nausea and Vomiting, Acupoint, Vagus nerve, Vestibular system, Double blind, Pediatric, Emetic

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1 Introduction

Acupuncture is a widely known non-pharmacological treatment modality that involves the insertion of thin (usually solid filiform) needles into strategic points (acupoints) in the body to achieve specific therapeutic effects. The needles are usually manually manipulated depending on the practitioner, to further stimulate the acupoint (1). Acupuncture has existed for thousands of years and is rooted in traditional Chinese medicine (TCM) concepts and theories (2). However, it is becoming increasingly common in other countries around the world; out of reports from 129 countries, 80% recognize the use of acupuncture (3).

Acupressure is a similar traditional Chinese therapy that incorporates the same acupoints but through a non-invasive procedure (4). Practitioners use their hands, elbows, feet, or special devices to apply pressure to acupoints (5). While not as common as acupuncture, acupressure has become an increasingly popular alternative for those seeking a less invasive treatment.

Additionally, research suggests that acupuncture and acupressure (acuthery) may be an appropriate and efficient treatment modality for chronic diseases (4). Thus, this would be especially beneficial in countries which are burdened by high rates of noncommunicable diseases. For example, cancer is the second leading cause of death globally; however, developed countries experience lower death rates than low- and middle-income countries (LMICs) despite having higher incidence rates of cancer. This may be due to the accessibility of treatment

options to the citizens in high-income countries (6). Therefore, there is a greater use of cancer treatment in these developed countries that does, however, involve adverse side effects and additional risks.

Acupuncture is known to have beneficial effects on various musculoskeletal injuries such as chronic ankle instability as well as neurological conditions such as migraines (7-8). There have also been increasing numbers of studies investigating the efficacy of acupuncture in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), a distressing side effect of chemotherapy that, if left unaddressed, occurs in more than 90% of patients undergoing highly emetogenic chemotherapy (9). Some of the most prominent factors determining the severity of CINV are the chemotherapy regimen, dosage, and patient characteristics. Side effects can include malnutrition, loss of appetite, and electrolyte and hydration disorders in patients (10). In addition, the effects of CINV can decrease patient compliance, leading to patient dropout. Experiences of CINV can decrease a patient's quality of life by impacting their social and physical well being.

Antiemetic drugs mitigate the effects of CINV, however, these are not without adverse side effects. The most commonly used antiemetic drugs are 5-hydroxytryptamine 3 receptor antagonists, neurokinin 1 receptor antagonists, corticosteroids, and olanzapine, an antipsychotic drug (11). The drugs have side effects such as headaches and fatigue that can further add to the distress of the patient as well as high costs that could prevent patients from

receiving the care they need (12). Additionally, ~ one-third of patients still suffer from CINV even when on antiemetic drugs (13). Therefore, non-pharmacological methods, such as acupuncture and acupressure, may play a role in the treatment of CINV.

The efficacy of antiemetic drugs may differ between adult and pediatric populations. However, most literature focuses on adult populations despite over 40% of children reporting that CINV is the most distressing side effect of chemotherapy (14). This indicates poor control of CINV in the pediatric population that needs to be further explored. Experiencing CINV affects the patient's quality of life and interferes with their ability to receive quality healthcare (15). Antiemetic medication has side effects such as mood disturbances that can have further adverse impacts on the patient's mental and physical health (16). In addition, understanding the anatomical and physiological mechanisms of how acupressure pinpoints specific acupoints that stimulate the nerve connections to reduce the nausea and vomiting reflexes is necessary to ensure that patients receive effective treatment. For example, the literature suggests that pericardium 6 (PC-6) and stomach 36 (ST-36) stimulate the vagus nerve directly, promoting parasympathetic activity and increasing gastric motility (17). Understanding exactly how the acupoints affect nausea and vomiting reflexes can lead to improved treatment options for children experiencing CINV.

There have been few trials and reviews conducted on acuthery and CINV in pediatric populations. Childhood cancers,

although relatively rare, should be examined separately from cancer in adults because they have different clinical behaviors, origins, and treatment modalities (18). In addition, cancer is still the leading cause of death in pediatric and young adult populations in the US (19) with a higher fatality rate in low- and middle-income countries (20). However, while there have been some studies on the impact that acupuncture and acupressure have on children experiencing CINV, these have not yet been summarized into a comprehensive review. Thus, the primary objective of this review was to provide a robust and comprehensive summary of the existing literature on the efficacy of acupuncture and acupressure to treat CINV, with a specific focus on youth aged five to eighteen years. The secondary objective was to evaluate how the acupoints' anatomical and physiological nerve connections impact nausea and vomiting reflexes. Additionally, this review proposes a representative clinical trial to address the continuing uncertainty about the magnitude of the sham acupuncture (placebo) effect in acuthery,

2 Discussion

2.1 CINV in children in high-income countries
Seventy-five percent (six out of eight) of the articles included in this review were published in high-income countries. Of these articles, three were published in the United States, two were published in Germany, and one was published in Taiwan.

Accessibility of acupuncture/acupressure and its portrayal as an option for children with CINV

In the United States, acupuncture and acupressure are often available as an additional treatment option and not as a standard of care. Although only 1.5% of the US population has used acupuncture, there has been a 257% increase in total licensed acupuncturists from 1988, demonstrating a significant increase in licensed and practicing acupuncturists (21,22). According to the US Bureau of Labor Statistics, there were approximately 7,800 acupuncturists employed as of May 2022 (23). The states with the highest number of acupuncturists include California, Florida, New York, and Washington (22). Although Washington has a high number of acupuncturists, acupuncture is not often offered as a standalone treatment option. For example, at the Seattle Children's Hospital, acupuncture is often a complementary treatment in addition to a primary treatment option (24). In fact, there was only one part-time acupuncturist and three physicians trained in acupuncture at the time the study was conducted (24). One study used a generalized estimating equations analysis to find that children were more likely to use acupuncture than adults, and that adolescents with a Hispanic mother were more likely to use acupuncture than non-Hispanic adolescents (25). The results also suggested that people in the working-class were less inclined to use acupuncture (25). There is not a breadth of statistics available on acupressure in terms of its prevalence. This may be because of varying license requirements to practice in the US (26). However, it can be inferred that while acutherapies have become increasingly popular, they still are not an option that many are presented with when they encounter health-related problems.

Financial restraints may also contribute to accessibility issues in the United States. Various private insurance plans such as Health Net, United Healthcare, and Aetna have covered acupuncture for many years (27). Some government-run programs including Medicare and the Veterans Administration also added acupuncture to their benefits in 2020. However, many insurance companies do not employ acupuncturists, as three US states have not officially recognized acupuncture as a valid and effective treatment option, which makes it difficult or impossible to bill them for their services (27). Additionally, out-of-pocket expenses for such therapies may not be affordable to the general public, thus furthering this inaccessibility.

Countries such as Germany and Taiwan utilize acutherapies more than does the United States. It is estimated that a third of German medical doctors utilize this therapy in their own practices (28). Another study based in Germany stated that acupuncture is the most prominent and popular complementary medicine treatment in the healthcare system (29). However, there is an association between the use of acupuncture and age; this suggests that it may not be presented as a common option for many children. Financially, acupuncture has been reimbursed by German health insurance since 2007 (30). Similarly, acupuncture services are covered by the National Health Insurance in Taiwan, and there was a higher prevalence of acupuncture usage (11%) in 2011 compared to the utilization in the United States (31).

Common acupoints used

In the articles reviewed, some of the most frequently used acupoints included the Stomach 36 (ST-36), Pericardium 6 (PC-6), and Large Intestines 4 (LI-4), which were referenced in 33% of the articles (16, 24, 32). All three of the articles that referenced these acupoints compared them with sham acupuncture and found that manipulating these acupoints reduced the occurrence of vomiting and the severity of nausea more so than in the control group, but two (Reindl et al., 2006 and Yeh et al., 2012) were unable to achieve a statistically significant outcome due to the limited number of participants. Another article found that the need for antiemetic medication and occurrence of vomiting was significantly lower in the intervention group than the control group (32). Other acupoints included five reflex points on the ear, in a form of auricular acupressure (14). However, these also led to ambiguous results due to the small study size. Finally, the last two studies used acupressure wristbands at the acupoint PC-6 but found that this was not more effective than placebo (33,34).

Responses to treatment and studies' limitations

In addition to evaluating the efficacy of acupressure and acupuncture, all six articles from high-income countries used a standard amount of antiemetic medication for all participants. Two of the articles demonstrated increased control of CINV from acupuncture and acupressure (24, 32). Another two found that acupressure was not more effective than the sham group (33,34). The last two articles found that patients in the intervention group reported lower severity and occurrence of nausea and vomiting (14, 16). However, the findings were not statistically significant which

was mostly due to the insufficient study size, thus not having enough statistical power to detect a difference, if there was one. Based on the power calculation, 35 participants were needed in the trial by Reindl et al., but due to attrition, only five patients were followed through to the end of the study. In addition to both studies not having sufficient sample size to achieve the desired statistical power, some other possibilities that precluded the achievement of statistical significance included the use of self-reported questionnaires in both studies, which were more prone to attrition, selection, and recall biases given their subjectiveness.

Failure to reach statistical significance could have involved other confounding factors in the two aforementioned studies. For example, in the study by Yeh et al., patients were divided into two groups (sham and intervention). In both these groups, auricular acupoints were stimulated in accordance with Dr. Huang's ear reflex theory (14). Auricular acupoints are rarely used to treat nausea and vomiting in the clinical setting. The acupoints in the intervention group included shenmen, sympathetic, cardia, stomach, and digestive subcortex (Table 1), which were known to treat nausea and/or vomiting according to Dr. Huang's ear reflex theory (Table 2); whereas the sham group stimulated acupoints that were not so known to treat nausea and/or vomiting (14). Given that the physiological pathways of the stimulated acupoint were undefined (Table 1), the statistically insignificant findings may have been due to the placebo effect in the sham acupressure group. For example, it may be difficult to blind participants during acupuncture research as it is difficult to

eliminate the sensation of a needle penetrating the skin (35). In the sham group, if participants were not properly blinded, they may have reported reduced nausea and vomiting because they believed they were receiving the intervention based on the sensation of skin penetration. This could have resulted in a smaller difference in the reduction of CINV between the sham and intervention groups, and given the insufficient sample size, there would not have been enough statistical power to detect such a small difference. Additional possibilities that may have resulted in statistical insignificance of the results are that the pediatric population may not be the most reliable as they may not be able to accurately recall the sensation of the acupuncture, or that the sensation of touch could vary greatly among this cohort. In the study by Reindl et al., since the acupuncturist was a human, results are subject to human errors. For example, placing the acupuncture needle in the wrong position or depth may cause the acupoint to not be stimulated adequately, which would alter or affect the results (Table 2). Additionally, given the randomized study design, Reindl et al. did not conduct an Intent to Treat or a Mixed-Effect Model analysis to ensure that the findings were robust (16).

The time of acuthery administration relative to chemotherapy could also impact its effectiveness. One study found that acupuncture performed 30 minutes before chemotherapy significantly reduced the frequency of CINV when compared to acupuncture performed after chemotherapy (36,37).

Table 1. Physiological pathways and their associated acupoints

Acupoints	Neural/muscular/hormonal/neurotransmitter pathways
ST36	Studies showed that electroacupuncture at ST-36 mitigates nausea and vomiting through a complex vagovagal pathway in rats (17). Acupuncture stimulates the sensory nerves at the ST-36 acupoint which travel through afferent nerve fibers to stimulate the dorsal motor nucleus of the vagus nerve, which controls involuntary movements of the digestive tract (17). This may promote gastric motility, which in turn reduces nausea (17, 38). This was further supported by a vagotomy in the rats, which completely abolished the increase in gastric motility that was observed after electroacupuncture at ST-36 (17). While this study focused on rats as test subjects, there have been some studies that show that the vagus nerve is stimulated in acupuncture in humans as well (39-43). One study found that electroacupuncture at ST-36 stimulated the sciatic nerve, which caused signals to be transmitted to the vagus nerve, although the mechanism as to how this occurs is unknown (41). However, many articles that have made this claim were not peer-reviewed.
PC6	Though the literature is sparse regarding the acupoint PC-6, scientists have reported that the acupoint PC-6 selectively activated areas of the cerebellum (the nodulus and uvula) that are specifically involved in vestibular control and alleviates symptoms of motion sickness and nausea (44-45). It has also been suggested that acupuncture at PC-6 facilitates the release of neurotransmitters which may desensitize responses of the chemoreceptor trigger zone or vomiting center in the medulla, thus resulting in decreased nausea and vomiting (45).

LI4*	The LI-4 acupoint is known to provide pain relief (46). However, based on non peer-reviewed literature, acupressure at the combination of both LI-4 and ST-36 was effective in preventing nausea (47). Additionally, peer-reviewed literature suggests that acupuncture at both PC-6 and LI-4 acupoints in conjunction with antiemetic drugs (in both the control and intervention group) reduced nausea intensity as well as postoperative nausea and vomiting (48). A similar study also found that acupuncture at PC-6 and LI-4 was more effective at reducing post-operative nausea and vomiting than acupuncture at PC-6 alone (49). Based on this information, the LI-4 acupoint may be effective in combination with other acupoints (ST-36 and PC-6) but more research is needed on the effectiveness of LI-4 alone when treating nausea and vomiting.
CV12*	CV12 has often been used in conjunction with PC6 and/or ST36 when treating nausea. On its own, it ameliorated digestion-related issues, such as bloating, constipation, and vomiting.
Auricular acupoints ⁺	This group of acupoints (shenmen, sympathetic, cardia, stomach, digestive subcortex) was cited in Dr. Huang's ear reflex theory (50). One physiological pathway to experiencing CINV is through the interaction of emetic drugs with dopamine receptors in the chemoreceptor trigger zone. This activates the nucleus tractus solitarius, which can initiate the emetic response. Thus, it is possible that the stimulation of auricular acupoints decreases the sensitivity of the dopamine receptors, thus decreasing the severity of the CINV.
BL20*	This acupoint has been traditionally used to treat digestion-related issues such as vomiting and emesis. It decreased xylazine induced emesis in dogs.
SP6*	The SP6 acupoint is most commonly used to treat labor or menstrual related pains but it was also effective in treating postoperative nausea and vomiting.
KD3*	This acupoint is usually used to treat sleep, energy, and weight irregularities. However, many articles that have made this claim are not peer-reviewed.

*There is no clear evidence on specific physiological pathways for these acupoints.

⁺There is no published evidence on the specific physiological pathway for these acupoints.

Table 2. Effectiveness of reducing CINV with acupuncture/acupressure versus conventional treatment

Study	Results	Acupoints	Timing of acutheraPy	Why findings may or may not have been effective
Yeh et al., 2012	Findings were not statistically significant between the acupuncture group and sham acupuncture group, with a	Auricular acupoints (shenmen, sympathetic, cardia, stomach, digestive subcortex)	The acupressure was given three times a day after receiving chemotherapy, as well as when participants felt nausea, for a	There is no scientific evidence supporting Dr. Huang's ear reflex theory being effective in reducing nausea and vomiting. However, it is possible that these acupoints were unsuccessful in modulating the sensitivity of the dopamine receptors (See pathological pathway for auricular acupuncture in Table 1). Since acupressure

	reduction in CINV in the intervention group.		total of seven days.	was administered after chemotherapy, this could have contributed to the statistical insignificance because it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV (Table 1.)
Reindl et al., 2008	Findings were not statistically significant between the acupuncture and control group but found that acupuncture could be effective at reducing CINV.	Acupoints were chosen by the acupuncturist to tailor to the patients' needs, most commonly used acupoints were PC6, ST36, CV12, LI4	Acupuncture was performed before starting chemotherapy and offered at consecutive days during the chemotherapy.	ST36 and PC6 may not have been stimulated enough to have modulated the vagus nerve, vestibular system, and/or neurotransmitter activity (See pathological pathway for PC6 and ST36 acupoints in Table 1). Administration of the acupuncture could be subject to human error, one of which could be misplacing the acupuncture needle close to the acupoint, thus causing the effects of the acupoints to be compromised. Although the acupuncture was administered before starting chemotherapy, the sample size was too small to detect any statistical significance between the two groups.
Ralston-Wilson, 2013	Findings were statistically significant and found that acupuncture decreased CINV.	ST36, LI4, KD3, SP6, PC6	Not available	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.) Although the timing of acupuncture was not available, starting the acupuncture before chemotherapy may have also contributed to the results.
Gottschling et al., 2008	Findings were statistically significant between the acupuncture treated and the acupuncture non-treated groups with a significant reduction in the need for antiemetics in the	PC6, ST36, CV12, LI4	Acupuncture was performed before starting chemotherapy and offered at consecutive days during the chemotherapy course based on the patient's demand.	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.) Starting the acupuncture before chemotherapy may have also contributed to the results as it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV

	acupuncture group.			(Table 1.)
Dupuis, 2018	Findings were not significant; acupressure wristbands did not reduce CINV in the acute or delayed phases.	PC6	Wristbands were worn starting at least 30 minutes before chemotherapy and continuously throughout the entire chemotherapy course and up to seven days after.	PC6 wristbands may not have exerted enough pressure to stimulate the pathways that the PC6 acupoint usually stimulates, regardless of when they were used. (See pathological pathway for PC6 in Table 1.) According to Sea-band® Australia, the brand of acupressure wristband that was used, the wristbands take 2-5 minutes to create an impact. Since the wristbands were worn before chemotherapy, they should have become effective during chemotherapy, further suggesting that the wristbands did not properly stimulate the physiological pathway of PC6 (51). Lastly, an insufficient sample size may have contributed to the insignificance of the findings because the authors did not enroll the minimum number of participants needed in each group.
Jones et al., 2008	Findings were not significant; acupressure wristbands did not cause a significant reduction in nausea or vomiting.	PC6	Wristbands were worn starting before chemotherapy and they were taken off after the conclusion of chemotherapy.	
Varejão et al., 2019	Findings were statistically significant, showing that laser acupuncture was effective at relieving nausea and vomiting	PC6, LI-4, ST-36, BL-20, and SP-6	The laser acupuncture was performed a few minutes before the start of chemotherapy.	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.) Starting the acupuncture before chemotherapy may have also contributed to the results as it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV (Table 1.)
Abusaad et al., 2015	Findings demonstrated that acupuncture significantly decreased nausea, vomiting, and	PC6	Participants were instructed to perform acupressure before starting chemotherapy	PC6 modulated the vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. (See pathological pathway for the PC6 acupoint in Table 1.) Starting the acupuncture before chemotherapy may have also contributed to

	retching.		and at least three times daily afterward.	the results as it might have provided more time for the acupressure to stimulate physiological pathways to reduce CINV (Table 1.)
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2.2 CINV in children in LMICs

Twenty-five percent (two out of eight) of the articles included in this review were published in LMICs. Of these articles, one originated in Egypt while the other, in Brazil.

Accessibility of acupuncture/acupressure and its portrayal as an option for children with CINV

The practice of traditional Chinese medicine in Brazil, including acupuncture and acupressure, began with the arrival of Chinese immigrants in the early 1800s (52). Since then, many immigrants and native Brazilians have participated in this treatment. According to data from the Federation of Acupuncturists of Brazil, there are ~160000 acupuncturists in Brazil (52). Despite the abundance of professional acupuncturists in Brazil, not all citizens utilize their services. Wealthy individuals, or those who have had a higher education and are covered by a private health plan, are more likely to use integrative and complementary practices such as acupuncture and acupressure (53). There is limited data available on acupressure regarding the utilization, the number of certified individuals, and the number of facilities that offer acupressure services, as acupuncture is much more commonly practiced in Brazil. In terms of financial accessibility, acupuncture is included in the health insurance provided by the Sistema Único de Saúde, Brazil's national health service (54). However, it is rarely used

compared to its usage with private health insurance (54).

In Egypt, there was only one acupuncture clinic in public hospitals as of 2016 (55). Although an increasing number of doctors have become more interested in acupuncture, there is no formal acupuncture educational training or legal regulations on its practice, which means there is no regulated and consistent way to learn or practice acupuncture (55). Additionally, it is not covered by medical insurance, furthering its inaccessibility to civilians (56). While there are numerous research articles published on acupressure and its effects in Egypt, there are no statistics regarding the prevalence of acupressure.

Common acupoints used

One hundred percent (two of two) of the articles from LMICs referenced the PC-6 acupoint in their intervention group, located on the inside of the wrist (57,58). However, one article also referenced the LI-4, ST-36, BL-20, and SP-6 acupoints (57). By referencing only one acupoint, the efficacy of that acupoint in treating CINV can be determined with relative unambiguity. However, using multiple acupoints allows acupuncturists to individualize the treatment plan according to the patient, which could lead to better results.

Responses to treatment

In addition to evaluating the efficacy of acupressure and laser acupuncture, all the

articles from LMICs used a standard level of antiemetic medication for all participants. The responses to the acutheraPy were positive in both studies. Varejão et al. found laser acupuncture to be effective at relieving nausea five days after chemotherapy as well as vomiting two and three days after chemotherapy (57). Abusaad et al. found that acupressure on the PC-6 point significantly reduced nausea, retching, and vomiting in the participants (58).

2.3 A direct comparison of high vs. LMICs: acupuncture/acupressure for children with CINV accessibility

Acupuncture and acupressure are becoming increasingly popular around the world, but of the countries included in this review, the United States is most prominent. The accessibility of acupuncture in Taiwan suggests that Asian countries which are in close geographic proximity to China are more likely to use traditional Chinese medicine such as acupuncture and acupressure. Similarly, Brazil, which has had an influx of Chinese immigrants since the 1800s, also has a higher prevalence of acupuncture (52). Additionally, Germany seems to have also deeply implemented this therapy into their healthcare system despite its more westernized culture. The only country that had significantly poor access to acupuncture is Egypt. However, the increasing number of studies published in Egypt suggests that acutheraPy may become more widespread in the future.

Financially, four of the five countries (USA, Germany, Taiwan, Brazil) include acupuncture in the public medical insurance. However, in

the US and Brazil, acupuncture is more commonly used in private medical insurance plans. In both these countries, financially able citizens are more likely to use acupuncture compared to marginalized and vulnerable populations, those living at or below the poverty threshold, who utilize other complementary therapies. Given that both private and public medical insurances cover acupuncture services, those with private insurance utilize these services more often (54). This could be due to that segment of the population having more knowledge and understanding of the benefits of acupuncture. Overall, while acutheraPy seems to be more popular among the wealthy, it is nonetheless becoming more widespread around the world.

Acupoints used

The most popular acupoint for treating CINV in children was the Pericardium-6 (PC-6) acupoint, which was referenced in five research articles (16, 24, 32, 57,58). However, there were various other acupoints that were commonly referenced such as Large Intestine-4 (LI-4) and Stomach-36 (ST-36), which were included in four articles (16, 24, 32, 55). These acupoints were also often referenced in studies on the efficacy of acupuncture on CINV in adults and seemed effective in preventing and minimizing the effects of CINV (59,60). The PC-6, ST-36, and LI-4 acupoints were also commonly used to treat nausea and vomiting even without the presence of chemotherapy (61). Thus, it is logical that these acupoints would be effective for treating CINV given that they are already used for treating nausea and vomiting.

Responses to treatment and studies' limitations

Of the eight studies included in this review, four studies found acupressure to be effective at preventing nausea and vomiting (24,32,57,58). Two studies saw positive effects of acupressure on CINV outcomes but due to their small study sizes and perhaps an inability to properly stimulate the acupoints (Table 2), these findings were not statistically significant (14, 16). Furthermore, two studies found acupressure to not be more effective than the placebo in preventing CINV (33,34). These studies both used acupressure wrist bands with acupoint PC-6. The PC-6 acupoint is commonly used amongst the other studies and has been shown to have beneficial effects in the prevention and treatment of CINV (16, 24, 32, 57,58). Thus, it can be inferred that acupressure wrist bands may not have exerted enough pressure to stimulate the PC-6 acupoint (33,34).

Evaluation of the neural pathways involved in triggering nausea and vomiting: Steps of neural pathway of acupoint

Studies have shown that electroacupuncture at ST-36 seems to mitigate nausea and vomiting through a complex vagovagal pathway in rats (17). Another study found that electroacupuncture at ST36 stimulated the sciatic nerve which can send signals to the vagus nerve (43) (Table 1).

Though the literature is sparse regarding the acupoint PC-6, scientists have reported that the acupoint PC-6 is involved in vestibular control and modulating the chemotherapy trigger zone, which may result in decreased nausea and vomiting (Table 1).

While the LI-4 acupoint is known to provide pain relief (46), there have not been many

studies evaluating the efficacy or physiological mechanism of the LI-4 acupoint alone on treating nausea and vomiting (Table 1). However, there is evidence that the LI-4 acupoint, when combined with PC-6 or ST-36, can increase their effects in reducing CINV (Table 1) (47-49).

3 Limitations

One of the most prominent limitations of this review is that there is not much research that has been conducted on the efficacy of acupressure for CINV in children. Therefore, literature was searched across multiple databases, such as the National Center for Biotechnology Information (NCBI) and Google Scholar for articles that may be available on one database and not the other. Additional literature was found by reading cited articles that were relevant to this topic.

The literature is also limited as it relates to the general accessibility of acupressure in the research setting (only one article described the accessibility). Therefore other content; including non-peer reviewed articles - was explored to find statistics on the accessibility of acupressure in relevant countries. However, while this was able to provide a general idea of the prevalence of acupressure, it may not accurately reflect the situation in the research setting.

Finally, there was a paucity of publicly available literature on certain acupoints (auricular acupoints) and their mechanisms as well as not enough peer-reviewed literature on the correlation of acupoint stimulation to the reduction in CINV. To mitigate this, non peer-reviewed articles were cited when the

information was consistent across multiple sources. Additionally, the physiological pathway of the auricular acupoints were inferred based on the publicly available literature.

4 Perspectives

Future research should first explore the accessibility of acuthery, more so in the research setting, as it provides insight into the prevalence and the standardization of this therapy. Second, researchers should consider focusing on specific acupoints to determine the efficacy of each point, instead of simultaneously using a variety of acupoints. Third, the physiological pathways and mechanisms of how stimulating acupoints such as LI-4, CV-12, and the auricular acupoints reduce nausea and vomiting should be explored. To incorporate the above recommendations, researchers would need to conduct more randomized control trials with larger patient populations to ensure sufficient statistical power to identify differences if they exist, and the impact of single-blinding and the placebo effect. An example of a randomized control trial to establish potential causal relationships is provided in the next section.

Thus far, evidence for the efficacy of acupuncture has been obtained using single-blind methods. Unmasked practitioners can hence inadvertently influence patients with their expectations, attitude and enthusiasm, thereby rendering the effectiveness of acupuncture controversial. The design of a double-blind needle was reported in 2007 but does not seem to have been utilized in subsequent studies (62). Contrary to medicines administered by the oral route, blinding to

patients is challenging in acupuncture therapy, because the the sensation of a needle penetrating the skin cannot be masked (as discussed above). However, patients must be counseled that this sensation may be irrelevant to therapy since it may only press against the skin (rather than penetrating it) (62).

Proposed clinical trial

To further the conversation and discussion about how to distinguish and disentangle the placebo effect from acupuncture, the following design for a double-blinded clinical study is proposed. In Table 3, 'sham' stands for a sham acupuncture procedure, +1 denotes an effect, 0 represents no effect, and 'pill' stands for a standard antiemetic dose. A double blind needle is used (62). The trial will consist of three arms (double blinded to both the practitioner and the patients; the patients will be counseled that the sensation of a needle is irrelevant, since it may only press against the skin, rather than penetrate it): Pill+sham acupuncture, Pill+acupuncture and acupuncture only. Acupuncture and sham acupuncture will be performed by a licensed acupuncturist to ensure that standardized acuthery is administered as well as to reduce human error.

The first row results imply that only the pill is effective, the second row results mean that only acupuncture is effective and the third row results mean that only sham (placebo) is effective.

This proposal will address the long standing conundrum about the placebo effect in acupuncture procedures. The clinical trial can be expanded and modified to include the timing of the therapies (relative to chemotherapy administration) employed as well. The results

from such a double-blind study will allow based interventions to reduce CINV in researchers/clinicians to implement evidence- children.

Table 3. Select results of proposed double-blind randomized clinical trial

Frequency, severity and duration of nausea and vomiting	Pill + Sham acupuncture	Pill + acupuncture	Acupuncture only
Only pill is effective	+1	+1	0
Only acupuncture is effective	0	+1	+1
Only placebo (sham acupuncture) is effective	+1	0	0

5 Conclusion

Given the evidence provided in the trial studies, acupressure and acupuncture may be effective options for the prevention and treatment of CINV in children. More specifically, acupoints PC-6, ST-36, and LI-4 were effective in controlling CINV whereas auricular acupoints were not. However, acupressure wristbands that target the PC-6 acupoint were shown to be ineffective based on findings from two studies (33,34). While acupuncture is becoming increasingly popular around the world as an alternative medicine, there are still accessibility barriers such as insurance coverage that prevents people from using this therapy. Additionally, while there is literature on how acupuncture at PC-6 and ST-36 reduce CINV, there remain many acupoints such as LI-4, CV-12, and auricular acupoints that have not been adequately researched with regard to the mechanism of their physiological pathways. Thus, future research should take into consideration the accessibility of acupoints to find its practical implications as well as focus on specific acupoints to determine their effectiveness. Researchers

should also conduct more trials of specific acupoints. Research studies with more participants are needed to provide adequate power to enable the detection of a statistically significant difference, if one exists, which will determine whether these therapies are truly effective in prevention and treatment of CINV in children. Furthermore, most of the existing literature incorporates the acupoints before chemotherapy, which resulted in statistically significant findings. However, more research that focuses on the time in which acupoints are administered is needed. This is because the trials that provided acupoints after chemotherapy found that the acupoints were less effective, indicating that timing may be a critical factor in determining effectiveness of acupoints. Finally, double-blinded trials are imperative to meet methodological standards in conventional medicine and to provide unequivocal evidence. Blinded needle designs are available and should be used along with pre-treatment patient counseling so that the trial is blinded to both the patients and the practitioners.

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