Journal of Research in Applied and Basic Medical Sciences 2021; 7(2): 76-85

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

Urmia University of Medical Sciences

Evaluation of the Effects of Cisplatin and the Cisplatin-Alum Mixture as Adjuvants for Increasing the Efficacy of Vaccination against *Salmonella Typhimurium* in Balb/c Mice

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Abstract

***Background & Aims*:** *Salmonella typhimurium* (*S. typhimurium*) is one of the causative agents of intestinal and extraintestinal infections in humans. Symptoms of the mouse infection by this bacterium mimic typhoid fever in humans. Adjuvants are compounds that enhance the effectiveness of vaccines in combination with them. Alum as an adjuvant causes a shift towards Th2 immune and strengthens the humoral immunity responses. Cisplatin is a highly effective anti-tumor drug that stimulates immune responses by activating macrophages and other immune cells and is used in tumor immunotherapy. This study aimed to investigate the role of cisplatin and the cisplatin-alum mixture as adjuvants to increase the efficacy of vaccination against *S. typhimurium* in Balb/c mice.

Materials & Methods: Male BALB/c mice were divided into five groups. Mice in the experimental groups received either the HKST vaccine alone or in combination with the adjuvants alum, cisplatin, or the cisplatin-alum. Mice in the negative control group received phosphate-buffered saline. All mice were immunized two times on days 0 and 14. Two weeks after the last immunization, immune responses to *S. typhimurium* were assessed by measuring the survival rate after challenge with a lethal dose of bacterium, bacterial load in the liver, interferon-gamma, and *S. typhimurium*-specific IgG1 and IgG2a production.

***Results*:** The number of colonies in the spleen and liver cultures in all dilutions was significantly lower in cisplatin-vaccine, and cisplatin-alum vaccine immunized mice. The average rate of specific IgG2a was higher in the same groups compared to other groups. The survival rate in alum-vaccine, cisplatin-vaccine, and cisplatin-alum-vaccine groups was significantly higher than in the control group. The average rate of Interferon-gamma in cisplatin-vaccine and cisplatin- alum vaccine groups was significantly higher than other groups.

***Conclusion*:** This study is the first to determine the role of administrating cisplatin and alum-cisplatin mixture on increasing the efficiency of the HKST vaccine in a mouse model. This study confirmed the role of cisplatin and cisplatin-alum mixture in increasing the efficiency of the HKST vaccine by using different experiments.

***Keywords*:** *Salmonella typhimurium*, vaccine, adjuvants, cisplatin, CDDP, alum

Received 13 June 2021; accepted for publication 23 September 2021

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[DOI: 10.52547/rabms.7.2.76]

Introduction

Infectious diseases are the second common cause of death after cardiovascular disease worldwide, but the first common cause of childhood deaths. Vaccination is the most effective medical interaction for preventing some infectious diseases (1). The golden age of vaccination started by Pasteur and Koch in the 19th century, and vaccination against bacterial pathogens was one of the most effective ways to eradicate or reduce the mortality and morbidity caused by bacterial infections in the past century (2). However, vaccines have not been entirely effective against all pathogenic bacteria. In the 21st century, new findings of functioning and features of the immune responses have shown new promising ways to improve the design, production, and delivery of more effective vaccines, which have increased the ability to induce the protective immune responses against a specific pathogen (3).

Adjuvants have been defined as substances that increase immunogenicity and efficacy of vaccines when added or mixed to them, resulting in more protective immune responses against infection (1, 4). Different types of adjuvants with different mechanisms of action are currently introduced, including mineral salts, emulsions, microparticles, cytokines, and microbial components, but considering the safety of adjuvants, only a few of them are licensed for human vaccination. At the moment, many adjuvants are used in research, and in many cases, their use is experimental (4, 5).

Alum is the only approved adjuvant with worldwide usage in licensed vaccines for humans. It has been shown that its adjuvant properties are related to the reduction of the release and degradation rate of the antigen and activation of the innate immune responses (6-9). However, alum preferentially induces T helper 2 (Th2) responses inducing antibody production. Still, protective immune responses against several life-threatening pathogens, primarily obligate and facultative intracellular ones, involve a Th1 immune response as well as antibody production. So, for vaccination against such pathogens, alum does not have enough efficacy, at least when used alone (4, 5, 10). Optimizing the immune responses using different adjuvant combinations that stimulate several signaling pathways seems logical (1).

Cisplatin (*cis*-diammine-dichloro-platinum (II) or CDDP) is a metal compound used successfully as a traditional anti-tumor drug in oncology. It cross-links the DNA of tumor cells, inhibits mitosis, and activates signal transduction pathways, leading to apoptosis and cell death (11, 12). On the other hand, the immunomodulatory effects of even small, sub-lethal doses of CDDP on cellular immune responses have been reported elsewhere (12). CDDP stimulates immune responses by activating macrophages and other immune systems. It increases MHC class I expression on host antigen-presenting cells (APCs) which is necessary for cytotoxic T cells (CTLs) activation (12).

CDDP promotes the accumulation and proliferation of effector cells, including macrophages, CD4+, and CD8+ T lymphocytes within the antigen milieu (12). It has been shown that CDDP treatment increased the monocyte-induced CD4+ proliferation, which was mediated mainly through the increased levels of Interferon (IFN)-β (13). In addition, CDDP increases the lytic activity of cytotoxic T-cells (14, 15) and reduces the immunosuppressive microenvironment, including immunosuppressive Tregs and other suppressor cells around the antigen (16-18).

Salmonella enterica serotype Typhimurium is a gram-negative rod-shaped, facultative anaerobic bacterium that usually causes self-limiting gastroenteritis in humans and systemic typhoid-like disease in mice. So, the mouse model of *Salmonella typhimurium* (*S. typhimurium*) infection has been used as a model for studying typhoid fever in humans (19). Induction of both humoral and cellular immune responses is necessary for protection against *S. typhimurium* infection (20).

The current study aimed to investigate the adjuvant activity of sub-lethal doses of CDDP (cisplatin), alone or in mixture with alum, as new vaccine adjuvants to induce immunity against *S. typhimurium* in Balb/c mice.

Materials & Methods

Mice: Male 6 to 8-week-old BALB/c mice were purchased from Razi Institute (Karaj, Iran) and were

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[DOI: 10.52547/rabms.7.2.76]

housed under pathogen-free conditions for one week before doing the experiments with free access to food and water. All experiments were conducted following the Animal Care and Use Protocol of Urmia University of Medical Sciences (Urmia, Iran).

Preparation of HKST: A heat-killed preparation of *S. typhimurium* (HKST) Persian Type Culture Collection (PTCC) 1735 was obtained, as illustrated before (5), with slight modifications. *S. typhimurium* PTCC 1735 was cultured overnight at 37±0.5°C on tryptic soy agar (TSA) (Merck, Germany) in anaerobic conditions. Cell mass from agar cultures was collected by centrifugation and washed by phosphate-buffered saline (PBS) (*50 mM, pH=7)* in triplicate. Cell pellets were resuspended in washing buffer and inactivated at 80°C for two hours. Heat-killed preparation was cultured on TSA to confirm the lack of bacterial growth. The 0.5 *McFarland* Nephelometer standard is used to adjust the turbidity of the HKST suspension at 590 nm. The HKST was stored at -70°C in disposable tubes. The optimal dose for immunization was determined in previous studies (5, 21).

Immunization protocol: CDDP solution was prepared by dissolving CDDP (Sigma- USA) in *PBS* and then filtered sterilized by 0.22 um filters. The injection dose was adjusted at 4 mg/Kg (the safe dose of CDDP for human use is 5 mg/kg) (22, 23).

The alum– CDDP-HKST mixture was prepared by thoroughly mixing CDDP solution with alum (aluminum phosphate, Sigma) and prepared HKST for an hour at room temperature (23). Immunization protocol, which was according to our previous studies (5, 21), is shown in Table 1. All mice were immunized subcutaneously in the neck twice, on days 0 and 14.

Table 1: Vaccination protocol in Balb/C mice

compounds / Immunized group	phosphate-buffered saline (PBS) µL	HKST (107 C.F.U. heat killed S.typhimurium)	Alum	CDDP
control	150	-	-	-
HKST*	100	50µL (10µg)	-	-
Al**-HKST	50	50µL (10µg)	50µL	-
CDDP***-HKST	50	50µL (10µg)	-	50µL (100µg)
Al-CDDP-HKST	-	50µL (10µg)	50µL	50µL (100µg)

*HKST: Heat-killed S. typhimurium

**Al: Alum

***CDDP: *cis*-diammine-dichloro-platinum

Removal of liver from *salmonella*-infected mice for determination of bacterial load:

The following procedure was done to determine the efficacy of each preparation in the induction of protective immunity against sub-lethal doses of pathogenic *S. typhimurium.* Two weeks after the second immunization (day 28), five groups of mice (each containing five mice) were injected intraperitoneally with 103 CFU of live pathogenic *S. typhimurium* PTCC 1735 suspended in 200 µl of PBS. Mice were sacrificed after forty-eight hours, and their livers were removed. After weighting, the whole organ was transferred into PBS containing 0.1% Triton X-100 and was homogenized individually. One hundredth (0.01) dilution of homogenates was separately cultivated on TSA for 24h in 37± 0.5°C. Colony-forming unit (CFU) counts were determined, and the log of CFU per gram was calculated.

Determination of IFN-γ Level:

Two weeks after the second immunization, five groups of immunized mice, each containing five mice, were used to determine the interferon-γ (IFN-γ) Level.

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In this respect, after mice were sacrificed, the spleens were removed and homogenized in RPMI 1640 medium (Gibco-BRL) supplemented with 10% fetal cow serum (FCS) (Gibco-BRL), penicillin (100 U/mL), and streptomycin (µg/mL) in aseptic conditions. Osmotic lysis was used to remove red blood cells using ammonium chloride buffer (NH4Cl 0.16M, Tris 0.17M). After washing with RPMI *Trypan Blue* exclusion method was used for cell counting. 10^6 spleen cells were cultivated in each well of a 24-well plate using supplemented RPMI 1640with FCS, penicillin, streptomycin, and 2-mercaptoethanol (5×105 M). Two wells were considered for each mouse. The cells were stimulated in vitro with 6×104 HKST. The optimal restimulation amount of HKST was determined according to our previous studies (5, 21). Microplates were incubated at 37°C in a *carbon dioxide* incubator (CO2, 5%). After 48h, supernatants were collected and stored at -70°C. The IFN-γ levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN).

Determination of IgG Subclass Responses by ELISA:

The levels of serum HKST-specific IgG1 and IgG2a antibodies were measured in five mice from each group using ELISAs (Enzyme-linked immunosorbent assays) in 96-well microtiter plates, two weeks after the second immunization (5, 24). Checkerboard titrations were used to optimize the ELISA conditions. 200 µL of HKST (containing 6×10^2 CFU) in coating buffer (0.1M carbonate, pH 9.5) was added into each well of the 96- microwell plate, then overnight incubation was done at 41°C. After three rounds of washing with phosphate-buffered saline (PBS), pH 7.4, containing 0.05% (vol/vol) Tween 20 (PBST), 5% bovine serum albumin (BSA) in PBST was added to block the remaining uncoated antigen for two h at 37±0.5°C. Then, 200mL of Serum samples (diluted 1/400 in PBST-BSA) were added to the wells, and incubation was done at 37±0.5 °C for two hours. After washing three times with PBST, plates were incubated with horseradish peroxidase-conjugated rabbit anti-mouse IgG1 or IgG2a (Serotec). After washing three times with PBST, 200mL of a TMB/H 2O2 substrate was added to each well to develop the reaction, then color development was terminated by the addition of 50mL of 2NH2SO4, and the absorbance was detected. Optical density at 450 nm (OD450) was measured using a spectrophotometer (CECIL- UK). Isotype antibody ratios (IgG2a/IgG1) were calculated based on ELISA results by dividing the OD values of IgG2a by those of IgG1.

Survival rate:

Two weeks after the second immunization, five groups of immunized mice, each containing six animals, were used to monitor the survival rate upon they were challenged intraperitoneally with a lethal dose containing 10^7 CFU of live pathogenic S. *typhimurium*. The survival rate was then monitored for 21 days. The lethal dose of *S. typhimurium* was determined in our previous studies (5, 21).

Statistical analysis:

Statistical analyses were performed using SPSS software version 22. To compare the levels of IFN-γ, IgG1, IgG2a, IgG2a/IgG1 ratio, and the bacterial load in the liver between groups, one-way analysis of variance (ANOVA) followed by Tukey's post hoc test were used. Kaplan-Meier test was used to compare the survival rate between groups. $p < 0.05$ was considered as statistically significant. A *95%* confidence interval was also considered.

Results

Determination of IFN-γ Level:

As shown in Figure 1, mice immunized with either CDDP-HKST or Al-CDDP- HKST vaccines produced significantly more IFN-γ than mice that received either PBS, the HKST alone, or Al-HKST. Lymphocytes from the mice vaccinated with CDDP-HKST produced significantly larger amounts of IFN-γ than those that received Al-CDDP-HKST, Al-HKST, HKST alone, or PBS (p=0.00 for all groups). Lymphocytes from the mice vaccinated with Al-CDDP-HKST produced larger amounts of IFN-γ than those that received Al-HKST(p=0.06), HKST alone(p=0.00), or PBS (p=0.00); however, the difference with the Al-HKST group was almost statistically significant (p=0.06). The mice immunized with the Al-HKST produced more IFN-γ

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than mice that received HKST alone; however, the difference between the groups was not statistically significant (p=0.53). The mice immunized with the Al-HKST produced more IFN-γ than mice that received PBS, and the difference was statistically significant (p=0.00), (Figure 1).

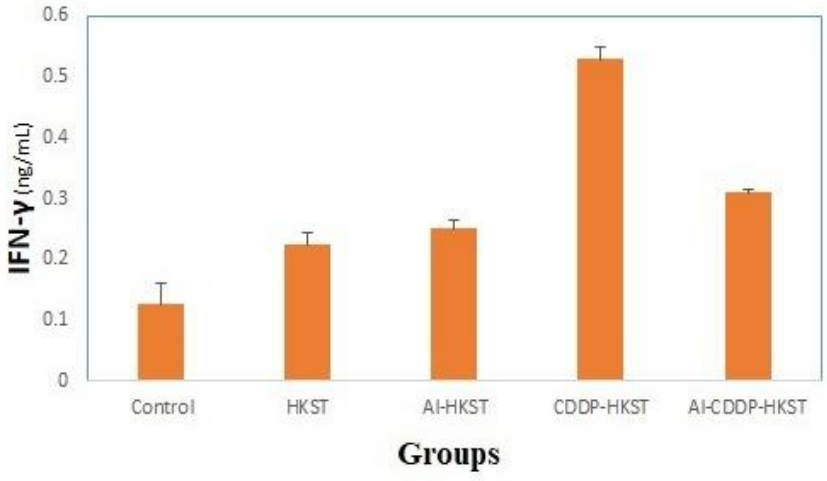


Fig 1: The effect of administering Al (alum)– CDDP (cis-diammine-dichloro-platinum)-HKST (Heat-killed S. typhimurium) mixtures on IFN-γ production. Two weeks after the second immunization, the spleens of individual mice (five per group) were removed, and IFN-γ production was measured and compared between the AL-CDDP-HKST (alum–CDDP mixture in combination with the HKST vaccine), control (PBS), HKST (HKST alone), Al- HKST (alum in combination with the HKST), and CDDP - HKST (CDDP in combination with the HKST vaccine) groups. Values are shown as the mean ± SE. For more details, please refer to the text.

Bacterial load in the liver:

Cultures of homogenized livers from the CDDP-HKST and Al-CDDP-HKST groups had significantly fewer mean bacterial colony counts than those of the control, HKST, and Al-HKST groups (p=0.000 for all groups). There was no significant difference between the mean liver colony counts of the CDDP-HKST and the Al-CDDP-HKST groups (Figure 2).

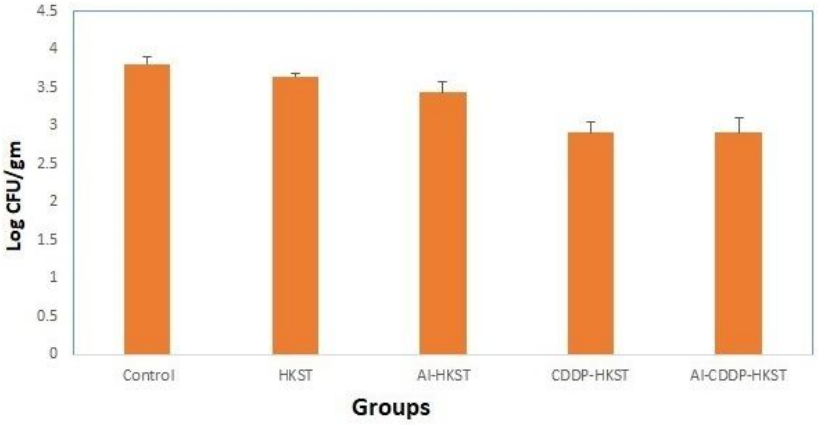


Fig 2: Bacterial loads in livers after challenge with sub-lethal doses (103 CFU) of live pathogenic S. typhimurium. Two weeks after the second immunization, the mice (five per group) were infected, and after forty-eight hours, the livers from each mouse were removed and homogenized individually. One-hundredth dilution of homogenates was cultured on TSA for 24h in 37± 0.5°C, then CFUs (log) were determined. Values represent the mean ± SE. For more details, please refer to the text.

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The survival rate after challenging with lethal doses of *S. typhimurium*:

Six mice in each group were challenged with lethal doses of pathogenic *S. typhimurium* two weeks after the last immunization. The survival rate of the mice was investigated every day for 15days post-challenge (Figure 3). The survival rate of mice in CDDP-HKST group was significantly higher than those observed in the control, HKST, or Al-HKST groups (p=0.006, 0.02, and 0.046, respectively). The survival rate of mice in Al-CDDP- HKST group was significantly higher than the survival rates observed in the control, HKST, or Al-HKST groups (p=0.006, 0.014, and 0.043, respectively). However, there was no significant difference between the Al-CDDP- HKST and CDDP- HKST groups regarding survival rate (p=0.939).

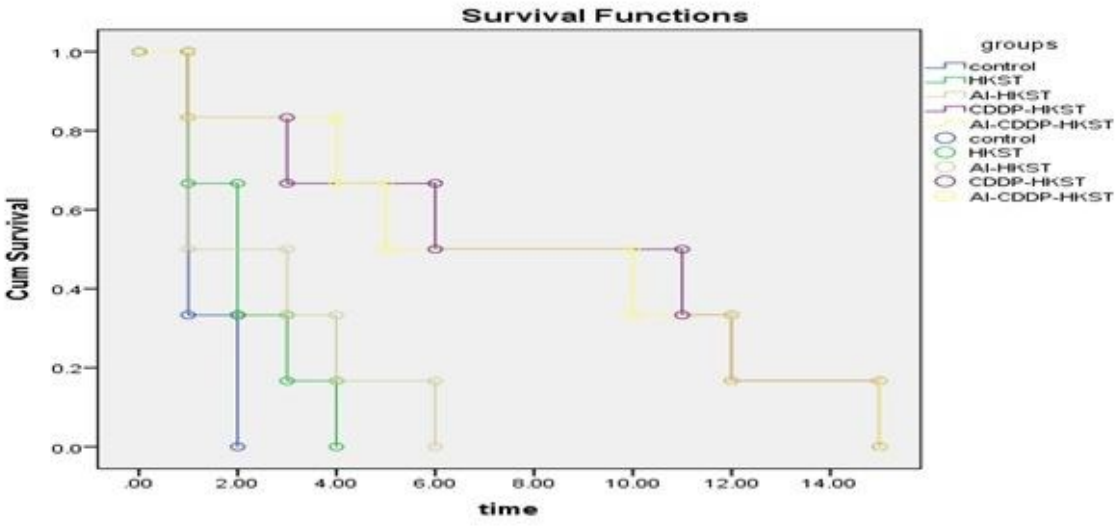


Fig 3: Survival rates of control (immunized with PBS), HKST (immunized with heat-killed *S. typhimurium*), Al-HKST (immunized with heat-killed *S. typhimurium* in combination with alum), CDDP-HKST (immunized with heat-killed *S. typhimurium* in combination with CDDP), and Al-CDDP-HKST (immunized with heat-killed *S. typhimurium* in combination with CDDP and alum). Two weeks after the last immunization, the mice were infected with a lethal dose of live pathogenic *S. typhimurium*. Their survival rate was recorded daily for 15 days. Mice in the CDDP-HKST and Al-CDDP-HKST groups showed a significantly higher survival rate than mice in the control group (p=0.006 for both). Mice in the CDDP-HKST and Al-CDDP-HKST groups showed a significantly higher survival rate than mice in the HKST group (p=0.02 and 0.014, respectively). Mice in the CDDP-HKST and Al-CDDP-HKST groups showed a significantly higher survival rate than mice in the Al-HKST group (p=0.046 and 0.043, respectively). Values are representative of six mice per group.

IgG isotyping:

Th1/Th2 cytokine profile is indirectly measurable by determining the isotype profile of IgG responses which is related to the cytokines produced by antigen-specific T cells. The relative amounts of anti-*S. Typhimurium* IgG2a to IgG1 antibodies were determined in the sera obtained from all groups two weeks after the final immunization.

As shown in Figure 4A, the IgG1 levels were significantly higher in the Al-HKST (p=0.00), CDDP-HKST (p=0.002), and AL-CDDP-HKST (p=0.001) groups compared with the HKST group. There was no significant difference between the Al-CDDP-HKST and CDDP-HKST groups regarding IgG1 amounts (p=0.976). The IgG1 levels in the Al-HKST group were significantly higher than all other groups (Figure 4A).

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IgG2a levels were significantly higher in the Al-CDDP-HKST group than in all other groups (p=0.00) (Figure 4B). The amounts of IgG2a were significantly higher in the CDDP-HKST group compared with the HKST group (p=0.00), but there was no significant difference in this respect with regard to the Al- HKST group (p=0.339). However, the IgG2a levels were significantly lower in the CDDP-HKST group than in the Al-CDDP-HKST group (p=0.000) (Figure 4B).

As shown in Figure 4C, IgG2a/IgG1 ratios were significantly higher in the Al-CDDP-HKST group than in the HKST (p=0.007) and Al-HKST (p=0.000) groups. The CDDP-HKST group had a significantly higher IgG2a/IgG1 ratio than Al-HKST (p=0.005). There was no significant difference between the Al-CDDP-HKST and CDDP-HKST groups regarding IgG2a/IgG1 ratio (Figure 4C).

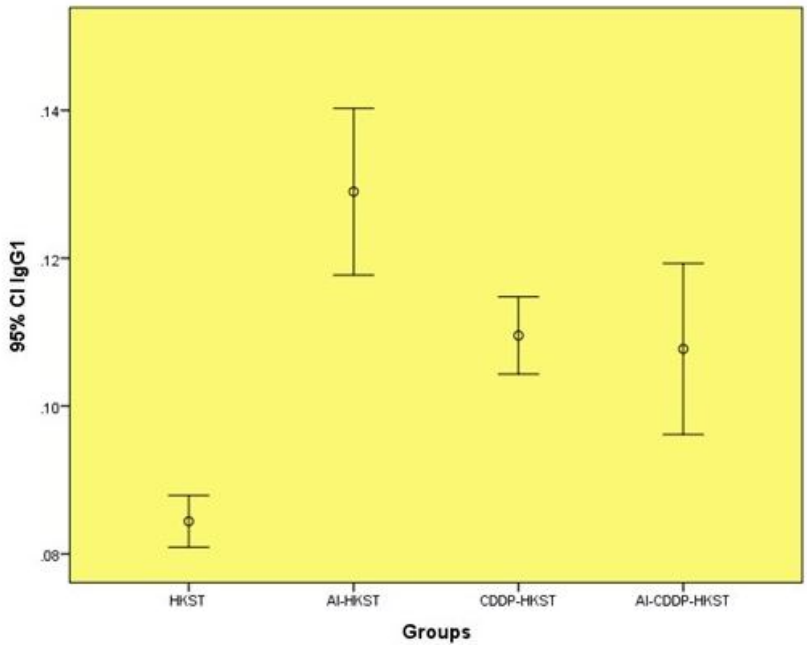


Fig 4A:

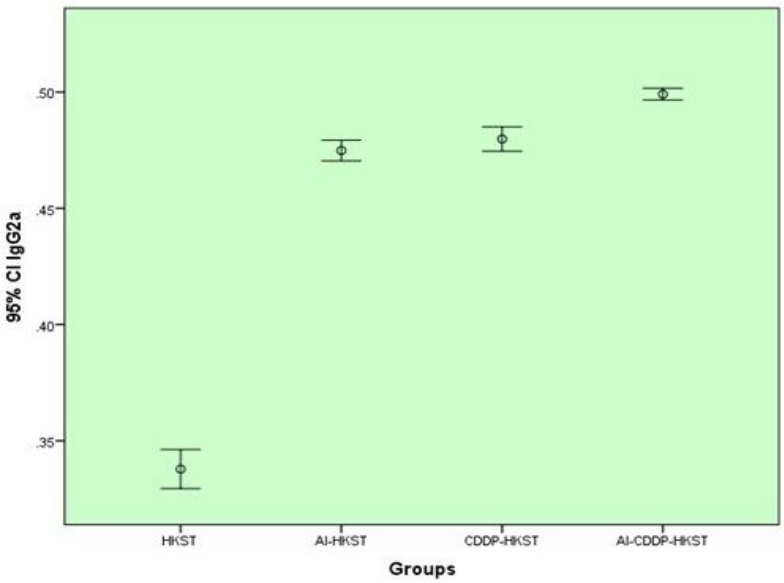


Fig 4B:

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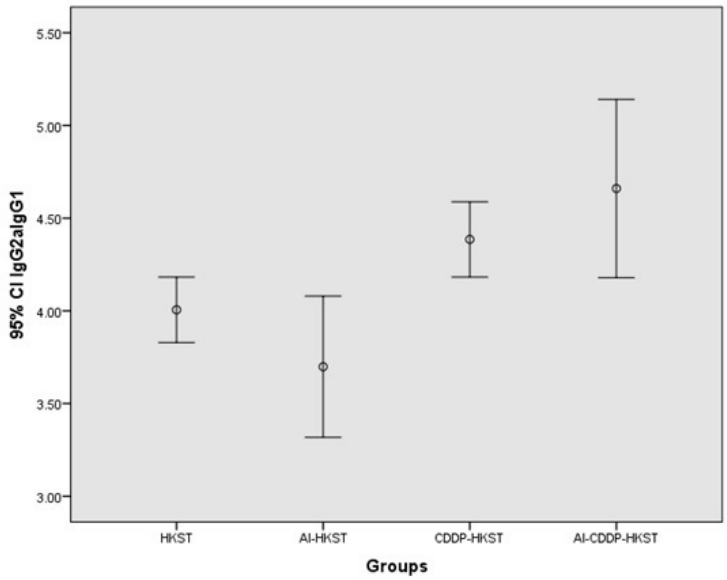


Fig 4C:

Fig 4: The effect of Al-CDDP-HKST administration on IgG isotyping. The amounts of anti-*S. typhimurium* IgG1(Figure 4A), IgG2a (Figure 4B), and the relative amounts of anti-*S. typhimurium* IgG2a to IgG1 antibodies (Figure 4C) in the sera obtained two weeks after the final immunization were determined. Values are shown as the mean ± SE. For more details, please refer to the text.

Discussion

S. typhimurium is an intracellular bacterial pathogen, which replicates inside and outside the cells of the reticuloendothelial system. Cellular immunity responses through priming of *S. typhimurium*-specific *CD8+* T *cells* have a crucial role in eradicating and controlling the infections caused by this bacterium (25); this should be taken into account in designing the vaccines against such microorganisms. Adjuvants provide better and broader protection against antigens that are co-administered with them (26). Alum is the most widely used adjuvant in human vaccines. However, alum-containing adjuvants have some limitations, for example, the inability to induce cell-mediated, especially $CD8^+$ T-cell responses (27, 28). So taking advantage of alum's capacity to induce a robust humoral response in combination with compounds to stimulate the cellular response is recommended to introduce an efficient vaccine adjuvant (28).

Our results showed that the CDDP (cisplatin) administration, when utilized as an adjuvant in combination with the HKST vaccine, significantly increased the vaccine's efficacy. The improved efficacy was associated with the following changes: the increased induction of IFN-γ, the increased production of *anti-S. typhimurium* IgG2a, more deviation toward aTh1 pattern of humoral immune response (by increasing IgG2a/IgG1 ratio); and improved resistance and survival against an *S. typhimurium* challenge. Using the CDDP-alum mixture instead of CDDP alone increased IgG2a production and Th1 pattern of the humoral immune response; however, it decreased the induction of IFN-γ and did not change resistance and survival against an *S. typhimurium* challenge. So, it can be concluded that using the CDDP-alum mixture as an adjuvant in combination with the HKST vaccine would increase the shifting of humoral immune responses toward Th1. So, the CDDP-alum mixture might be a good adjuvant to be co-administered with vaccines against pathogens that need both humoral and cellular immune responses.

Our findings of the adjuvant activity of cisplatin (CDDP) align with Bialkowski et al.'s study. They showed that cisplatin treatment significantly increased

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the efficacy of immunizing with mRNA encoding the HPV16 E7 oncoprotein and TriMix for female genital tract tumors in a mouse model (29). Our results also agree with Kaur et al.'s that an in vivo antileishmanial study showed cisplatin at low dose decreased parasite burden and increased delayed-type hypersensitivity response (30). Furthermore, Joshi et al.'s study showed that chemotherapy of leishmaniasis in Balb-c mice with cisplatin produced a strong Th1 immune response responsible for the resolution of the disease (31). This finding agrees with our results that CDDP (cisplatin), as an adjuvant for HKST vaccine, induced Th1/cellular responses crucial for an efficient immunity against *S. typhimurium* (20).

In conclusion, administering cisplatin or cisplatin-alum mixture as adjuvants combined with an HKSL vaccine shifted the immune response to a Th1 profile and enhanced immunity against *S. typhimurium*.

Up to our knowledge, this is the first study to show the adjuvant activity of Cisplatin and Cisplatin-alum mixture for a prophylactic vaccine against a microbe. As Cisplatin has been approved for human use (32), it, alone or in mixture with alum, may provide a new, relatively safe adjuvant for eliciting effective vaccine-induced Th1 immune response to microbes.

Acknowledgments:

This work was supported by the Deputy of Research and technology of Urmia University of Medical Sciences, Urmia, Iran [grant number: 92-01-32-1208].

Conflict of Interest:

The authors declare no conflict of interest.

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[DOI: 10.52547/rabms.7.2.76]