Oxytocin as a protective agent in cisplatin ototoxicity in rat model

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* **Ototoxicity** is inner ear dysfunction caused by a drug or chemical agent resulting with hearing loss, imbalance or both.
* Reversible/irreversible
* **Cisplatin** is a potent antineoplastic drug commonly used in the treatment of cancers of testis, ovary, cervix, bladder, lung and head and neck, medullablastom, neuroblastom, osteosarcom.\(^{(1)}\)
* **Dose limiting** major side effect of cisplatin is **ototoxicity**.\(^{(2)}\)
Cisplatin (CP) entry into outer hair cell results in cell death, which appears to be primarily caspase-dependent. The steps that may be involved include: (1) CP entry into the outer hair cell through mechanotransducer channels; (2) CP within cells can be aquated to form the monohydrate complex (MHC), which is more highly reactive; (3) CP and/or MHC can activate NOX-3, resulting in ROS production; (4) ROS may, in turn, activate JNK; (5) these molecules can translocate to the cell nucleus to activate genes involved in the cell death pathway; (6) these genes can then translocate to the mitochondria, causing (7) the release of cyt c, which can trigger (8) apoptosis via caspase-dependent mechanisms.
* Ototoxicity of cisplatin characterized with irreversible progressive bilateral high frequency hearing loss and tinnitus.
* Hearing loss starts at high frequencies (4000-8000 Hz), and progresses to lower frequencies which is important for speech recognition.(2,3,4)
* %60-80 of patients have elevated threshold levels whereas %15 of patients have significant irreversible hearing loss.(5,6)
Cisplatin causes

* Progressive outer hairy cell loss from base to apex and atrophy in stria vascularis.
* Production of reactive oxygen species (ROS) and inhibition of antioxidant enzymes as superoxid dismutase, catalase and gluthation which results in accumulation of hidrogen peroxide and toxic lipids.
* Ca influx into outer hairy cell lead to apoptosis and cell death. (7,8,9)
Many studies to prevent from cisplatin ototoxicity are based on antioxidant agent. (9-12)

But most of these agents reduce antitumoral effect of cisplatin. (13)

Today, there is no optimum agent that reduce cisplatin ototoxicity without any adverse effect on antitumoral activity.
Oxytocin is a nanopeptide hormone increasing in pregnancy. In recent studies, antioxidant and antiinflammatory effects are shown in animal models especially in cisplatin nephrotoxicity. (14-17) Oxytocin reduces consumption of glutathion and SOD, inhibits NADPH oxidase and myeloperoxidase, elevates NO levels, prevent apoptosis and inflammation. (18,19,20) Also transcripts of oxytocin receptors are shown in rat inner ear. (21)
There is no research about the effect of oxytocin on cisplatin ototoxicity in literature until today.

In our study, protective effect of oxytocin in cisplatin ototoxicity either with intratympanic (IT) and systemic route (IP) is investigated and compared with distortion product otoacoustic emission (DPOAE).
**Material and Method**

- 24 healthy female adult wistar albino rat weighing 190-300 gr were included.
- Rats were housed in an environment with light cycle (12 h light, 12 h dark) at 25°C temperature.
- General anesthesia was given intraperitoneally using 90 mg/kg ketamine and 10 mg/kg xylazine.
- All rats were examined with operating microscope for presence of otitis or wax and tested with DPOAE to evaluate hearing before any drug administration.
- The animals showing the presence of DPOAE were used in the experiment.
Rats divided into 4 groups*
* Group 1- IT salin +IP saline
* Group 2- IT saline + IP cisplatin
* Group 3- IT oxytocin+ IP cisplatin
* Group 4- IP oxytocin+ IP cisplatin

*IT intratympanic, IP intraperitoneal
After baseline DPOAE measurements between 2000 and 9000 Hz for all groups,

**Group 1** - 0.1-0.3 ml IT saline through a 28 gauge dental needle from anterosuperior quadrant+IP saline for 4 days.

**Group 2** - 0.3 ml IT saline for 4 days +20 mg/kg cisplatin divided into two doses given at first and second day as a slow infusion IP.

**Group 3** - 0.3 ml IT oxytocin (5 IU/5ml) for 4 days+cisplatin as Group 2

**Group 4** - 1mg/kg oxytocin for 4 days-cisplatin as Group 2&3
After one day waiting for the clearance of liquids from middle ear cavity, DPOAE measurements were done at 5th day.

Pre- and posttreatment DPOAE measurements were compared.

Results were analyzed statistically with SPSS 15.0

p<0.05 is accepted as statistically significant.
Results

- Group 1
- Statistically significant reductions were found in pre and post treatment DPOAE amplitudes except 2730 frequency.
- Difference is lower than other groups.
- Due to traumatic IT application?
* Group 2
* Statistically significant DPOAE amplitude reductions were found in all frequencies (2–9kHz)
* Difference is highest.
* Severe ototoxic effect of cisplatin.
* Group 3
* When compared with group 2, DPOAE amplitude reductions are smaller in group 3 (statistically significant in 3218, 3825, 4549, 6367, 7604 Hz)
* When compared with group 1, no statistically significant amplitude reduction is seen in group 3
* **Group 4**

* When compared with group 2, DPOAE amplitude reductions are smaller in group 4 (statistically insignificant in 5434, 6367, 7604 Hz).
Cisplatin is a potent antineoplastic agent with ototoxic side effect which causes dose limitation.

Ototoxicity is originated from free oxygen radicals production in the outer hair cell, spiral ganglion stria vascularis and in the cochlea.

Endogenous antioxidant defence mechanisms are insufficient to counteract cisplatin.

Application of exogenous antioxidants become primary focus in the treatment strategy of cisplatin ototoxicity.
A variety of antioxidant molecules are studied,

- vitamin E (22)
- vitamin C (23)
- Resveratrol (24)
- sodyum tiyosulfat (25)
- D- ya da L-metionin (26)
- lipoik asit (27)
- N-asetil sistein (28)
- aminoguanidin (29)
Several studies show antioxidant and antiinflammatory effects of oxytocin (OT) in animal model.

Subcutaneous injection of OT on wound healing and animal sepsis model has antioxidant effect, and it changes immun and antiinflammatory response. (30,31)

Intraperitoneal OT treatment protects renal injury with its antiinflammatory effect. (18,19,20,32)

There is no publication about protective effect of OT on cisplatin ototoxicity, neither with systemic or IT route.
Due to DPOAE amplitude changes in our study,

* Both IT and IP injection of oxytocin provide protective effect on cisplatin ototoxicity.
* IT route show statistically significant protection at 3218,3825,4549,6367,7604 Hz frequencies.
* IP route show show statistically significant protection at 5434,6367,7604 Hz Hz frequencies.
* IT route show better results than IP route but this is not statistically significant.
* Cisplatin leads damage to outer hair cells starting from basal turn.
* OAE evaluate the state of contraction of outer hair cell so we used DPOAE as a non-invasive simple method that reflects functional state of these cells(33) and detect the effects of cisplatin on the cochlea before changes are detected by pure-tone audiometry(34)
* So we used DPOAE to detect ototoxicity.
Clinical use of antioxidants has always been limited due to negative interactions with the chemotherapeutic drugs. They can reduce effectiveness of antineoplastic agents. Local administration of antioxidants prevents systemic absorption, so efficacy reduction of cisplatin will be avoided.
Oxytocin & cisplatin interaction is mysterious.

Oxytocin has systemic side effects as hypotension, tachycardia, ECG changes and with high doses water intoxication due to antidiuretic effect.

IT administration is safe and easy method to reach high drug concentration in inner ear without systemic side effect.
New studies are needed for
* protective effect of oxytocin in cisplatin ototoxicity,
* presence of oxytocin counterreaction with cisplatin
* presence of oxytocin receptor in human inner ear
* and dose of IT oxytocin.
Thank you...