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## Chemical Substances Used in the Treatment of Ganglions Located in the Hand and Wrist

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

### Abstract

The aim of this work was to compare different chemical substances used in the treatment of ganglions located in the hand and wrist region. Their basic properties and mechanisms of action have been described. Moreover, the risks associated with the use of particular substances have been highlighted and potential complications connected with their administration have been discussed. On the basis of the available literature, the results of ganglion aspiration treatment followed by an injection of a chemical substance into the cyst cavity have been assessed. In the authors' opinion, due to the existing risk of complications associated with this treatment, as well as the relatively high rate of ganglion recurrence, this procedure should only be performed by qualified medical personnel. The authors recommend observation in cases of asymptomatic ganglions of the hand and wrist, and operative treatment in cases in which pain, restriction of limb mobility and weakening of handgrip strength are observed (**Polim. Med. 2016, 46, 1, 95–100**).

**Key words:** steroids, wrist, hand, ganglion cysts, hyaluronoglucosaminidase.

Methods of treatment for ganglions located in the hand and wrist region include observation, surgical removal of the lesion and aspiration, which may or may not be followed by an injection of a chemical substance into the cyst cavity [1–4]. Historical methods, such as causing the rupture of a ganglion by applying pressure to it with a golden coin, smashing the lesion with a heavy book (including the Bible) or applying digital pressure to the cyst are no longer in use [1, 3]. This article discusses the range of chemical substances most commonly used in the treatment of ganglion cysts located in the hand and wrist region in clinical practice.

## Chemical Substances

### Hyaluronidase

Hyaluronidase is a protein enzyme from the family of hydrolases that depolymerizes hyaluronic acid. It also causes an increase in the permeability of connective tissue. Due to these properties, hyaluronidase is used

in medicine to augment the dispersion and absorption of other injected substances and liquids. However, decreases in tissue viscosity may facilitate the spread of microorganisms, thus increasing the risk of infection. A variety of hyaluronidase preparations are commercially available: Hydase<sup>TM</sup> (Prima-Pharm Inc.), Vitrase (Bausch + Lomb Inc./Valeant Pharmaceuticals International Inc.), Amphadase (Amphastar Pharmaceuticals Inc.) and Hyason (Organon Pharmaceuticals). These products are available in 1–1.2 mL vials containing 150–200 international units (IU) of the enzyme per milliliter. Synthetic human hyaluronidase containing 150 IU/mL, named Hylenex (Halozyme Therapeutics), was approved for use in 2005. The administration of hyaluronidase is associated with the risk of an allergic reaction. Subjects who are allergic to bee or wasp venom have a higher risk of developing an allergic reaction. Complications and side effects observed after the administration of hyaluronidase include edema and erythema at the injection site, hypotonia, seizures, dizziness, shivers, nausea, vomiting and tachycardia [5]. A skin allergy test is recommended before hyaluronidase

dase administration. Hyaluronidase can interact with other medications. In cases of simultaneous administration of local anesthetics (e.g. lidocaine) and hyaluronidase, the risk of hyaluronidase side effects is elevated. Antihistaminic drugs, cortisone and salicylates have the potential to weaken the activity of hyaluronidase, while hyaluronidase may attenuate the efficacy of benzodiazepines, furosemide and fenytoine. The duration of action of hyaluronidase in the human body varies between 24 and 48 h.

The fluid found inside ganglion cysts is composed of glucosamine, albumins, globulins and above all of hyaluronic acid [1]. The idea of using hyaluronidase in the treatment of ganglion cysts is based on the assumption that breaking down the polymeric bonds of hyaluronic acid will result in thinning the fluid inside a ganglion and thus will make the aspiration of a cyst easier [1] (Fig. 1). Otu [6] used hyaluronidase injections before ganglion aspiration in the treatment of 349 cysts in 340 patients, and reported 95% good results in a six month observation period. Paul and Sochart [7] compared the results of treatment in two groups of 35 subjects each. Patients in the first group were subjected to ganglion aspiration and methylprednisolone administration, while in the second group these procedures were preceded by hyaluronidase injections. In two years of follow-up, the healing rates were 57% for the first group and 89% for the second group [7]. Jagers op Akkerhuis et al. [8] conducted a prospective randomized clinical trial in which they compared the outcomes in patients who had undergone surgical excision of ganglions with those who had had hyaluronidase injections and cyst aspiration. The study was conducted on 100 patients divided into two groups of 50. After one year, the authors assessed the results in 43 of the

patients who had undergone surgical treatment and 46 of those treated conservatively. The recurrence rate after surgical excision was 24%, while in those treated conservatively it was 77% [8]. A similar study was conducted by Hajer et al. [9], who analyzed a group of 32 patients, of which 12 were operated on and 20 were treated conservatively, with hyaluronidase injections and ganglion cyst aspiration. In a six-month observation period, ganglions recurred in 25% of the patients treated surgically and in 85% of the patients who had undergone ganglion cyst aspiration [9].

Unlike all of the above-cited studies, in which hyaluronidase administration preceded ganglion aspiration, in the clinical trial conducted by Chatterjee et al. [10], hyaluronidase, triamcinolone or sodium tetradecyl sulfate were injected after aspiration. The study group consisted of 180 patients, divided into three subgroups of 60 patients each. After aspiration, the needle was left inside the cyst and a separate syringe was used to inject 2 mL of one of the three tested substances. This procedure was repeated three times at one-month intervals. After a minimum follow-up period of six months (the longest follow-up lasted 18 months), the authors assessed the results of the treatment and reported the following recurrence rates: 20% in the triamcinolone group, 31.6% in the hyaluronidase group and 35% in the sodium tetradecyl sulfate group. In the hyaluronidase group, two patients (3.33%) developed a hypersensitivity reaction, and in one patient (1.67%) hyaluronidase administration caused skin ulceration at the injection site. Hypopigmentation of the skin was not observed in any of the patients [10].

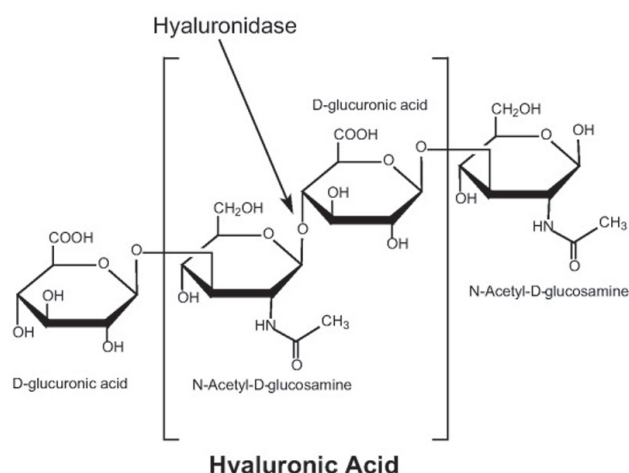
## Steroids

Cortisol (hydrocortisone) is an organic chemical compound with the molecular formula  $C_{21}H_{30}O_5$  and molar mass 362.47 g/mol. It is a natural steroid hormone produced by the zona fasciculata of the adrenal cortex (Fig. 2).

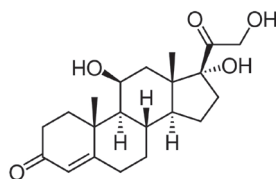
Triamcinolone is an organic chemical compound with the molecular formula  $C_{21}H_{27}FO_6$  and molar mass 394.43 g/mol. This fluorinated corticosteroid is a synthetic derivative of prednisolone (Fig. 3).

Methylprednisolone is an organic chemical compound with the molecular formula:  $C_{22}H_{30}O_5$  and molar mass 374.47 g/mol. It is a synthetic corticosteroid and a methylated derivative of prednisolone (Fig. 4).

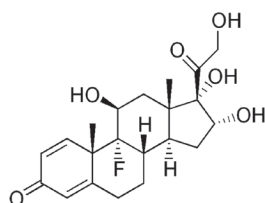
These chemical substances exert an anti-inflammatory effect, the intensity of which is dependent (among other things) on the dose administered. Five mg of prednisolone, 4 mg of methylprednisolone, 4 mg of triamcinolone and 20 mg of hydrocortisone exert an anti-inflammatory response of equal intensity. Topical use of steroids is connected with the risk of pectchie, ecchymoses, skin atrophy and skin discoloration. Moreover, allergic reactions and hypersensitivity



**Fig. 1.** The mechanism of action of hyaluronidase on hyaluronic acid. Hyaluronidase is a protein enzyme from the hydrolases family that depolymerizes hyaluronic acid by breaking down beta-1-4 linkages between N-acetyl-D-glucosamine and D-glucuronic acid



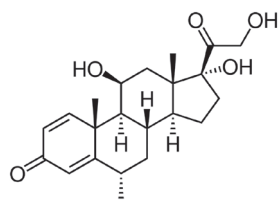
**Fig. 2.** The structural formula of cortisol (hydrocortisone) – a natural steroid hormone produced by the zona fasciculata of the adrenal cortex. Systematic name: (11 $\beta$ )-11,17,21-trihydroxypregna-4-ene-3,20-dione; molecular formula:  $C_{21}H_{30}O_5$ ; molar mass 362.47 g/mol



**Fig. 3.** The structural formula of triamcinolone – a fluorinated synthetic derivative of prednisolone. Systematic name: (11 $\beta$ ,16 $\alpha$ )-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione; molecular formula:  $C_{21}H_{27}FO_6$ ; molar mass 394.43 g/mol

to steroids can also be observed. Topical use of steroids is also associated with an elevated risk of infection.

Steroids were first introduced for the treatment of ganglions by Becker in the 1950s [1]. In the 1960s, Derbyshire used hydrocortisone in 22 patients, obtaining satisfactory results in 86% of them after follow-up periods ranging from two months to five years [11]. Hydrocortisone was also used by Holm and Pandey in the 1970s [12]. In time, hydrocortisone was replaced with synthetic derivatives of prednisolone (methylprednisolone, triamcinolone). In a prospective randomized study, Valrey et al. [13] compared the results obtained after ganglion aspiration alone and after aspiration combined with injection of 1 mL (40 mg/mL) of methylprednisolone. After a mean follow-up period of one year, recurrence was observed in 67% of the patients in both groups [13]. The same dose of methylprednisolone was used in one of the patient groups in a study by Nasab et al. [14]. This prospective study was conduct-



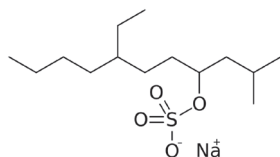
**Fig. 4.** The structural formula of methylprednisolone – a methylated synthetic derivative of prednisolone. Systematic name: (1S,2R,8S,10S,11S,14R,15S,17S)-14,17-dihydroxy-14-(2-hydroxyacetyl)-2,8,15-trimethyltetraacyclo[8.7.0.0.2,7.0.11,15]heptadeca-3,6-dien-5-one; molecular formula:  $C_{22}H_{30}O_5$ ; molar mass 374.47 g/mol

ed on 66 patients: 24 had their ganglion cysts aspirated, in 20 patients aspiration was combined with injection of methylprednisolone, and in another 22 patients aspiration was followed by administration of 1 mL of 76% ethanol. After 12 months of observation, ganglions recurred in 62.5% of the patients in the first group, 45% of the subjects in the second group and 36.5% of the patients in the third group [14]. Limpaphayom and Wilairatana [15] compared the outcomes of surgical treatment of dorsal wrist ganglions with the results of aspiration combined with injections of methylprednisolone (1 mL; 40 mg/mL). The results were assessed after six months in the 11 patients treated surgically and in 13 patients who underwent conservative treatment. Recurrences were observed in two out of the 11 surgically-treated patients (18.2%) and in eight of the 13 patients in the group managed with aspiration and methylprednisolone injections (61.5%) [15].

Triamcinolone was used by Colberg et al. [16] in the treatment of ganglions of the wrist in children. The study group consisted of 21 children (14 girls and 7 boys; mean age 7.2 years) with asymptomatic ganglion cysts that had been present for at least one year prior to inclusion in the study. After a mean follow-up period of 2.5 years, ganglion recurrence was observed in three children (14%) [16]. The effect of triamcinolone treatment of ganglions in adults was studied by Paramhans et al. [17]. The aim of the prospective study conducted by this team was to compare the outcomes of surgical resection of ganglions with the results of ganglion aspiration and injections of 2 mL of 10% triamcinolone. The study included a total of 219 patients, out of whom 114 were treated surgically and 105 were treated with aspiration and steroid injections. The ganglions were located in the wrist region, predominantly on its dorsal side (82%). In the two-year observation period, ganglion recurrence was noted in eight out of the 105 patients in the group treated with aspiration (8.4%) and in 14 out of the 114 patients who were treated surgically (12.2%). In this study no adverse effects, including skin hypopigmentation, were observed after administration of triamcinolone [17]. This was in contrast to the aforementioned study by Chatterjee et al. [10], who reported hypopigmentation in five out of 60 patients (8.3%) who were treated with triamcinolone.

### Sodium tetradecyl sulfate (7-ethyl-2-methyl-4-undecanyl sulfate sodium salt)

Sodium tetradecyl sulfate is a chemical compound with the molecular formula  $C_{14}H_{29}NaO_4S$  and molar mass 316.43 g/mol (Fig. 5). This substance is used in sclerotherapy for varicose veins of the lower extremities and esophageal varices. It was introduced into clinical practice by Reiner in 1946. The following preparations of sodium tetradecyl sulfate are currently available on the



**Fig. 5.** The structural formula of sodium tetradecyl sulfate – an anionic surfactant. Systematic name: sodium 7-ethyl-2-methyl-4-undecanyl sulfate; molecular formula:  $C_{14}H_{29}NaO_4S$ ; molar mass: 316.43 g/mol.

market: Aethoxysclerol (Kreussler Pharma), Fibrovein (STD Pharmaceutical Products Ltd.) and Sotradecol (Elkins-Sinn Inc.). Solution concentrations range from 0.1% to 3%. Local adverse effects after administration of this agent include pain, reddening of the skin immediately after injection, secondary skin discoloration and ulceration [18, 19]. Serious systemic complications, such as pulmonary embolism, cardiac arrest and distal limb necrosis, have also been described [18, 19].

Sodium tetradecyl sulfate was used in the treatment of ganglions by Mackie et al. in the 1980s [20]. The recurrence rate three months after its use was as high as 93%. Moreover, the authors emphasized the possible risk connected with inadvertent injection of this agent into a tendon or a joint [20]. Chatterjee et al. [10] observed hypersensitivity to sodium tetradecyl sulfate in four of their 60 patients (6.66%) and the presence of skin ulcerations in three (5%).

## Other Chemical Substances

A number of other chemical substances used in the treatment of ganglion cysts deserve to be mentioned. These include antibiotics (tetracycline), alcohols, phenols, local anesthetics (lidocaine, xylocaine) and hypertonic salt solution [2, 14, 21–23].

Tetracycline was used by Ashindoitang in the treatment of ganglions in 20 patients aged from 20 to 70 years. The majority of lesions were located on the dorsal surface of the wrist (80%). After ganglion aspiration, 1 mL of tetracycline (100 mg/mL) was injected into the cyst cavity. Equal volumes of medication were administered to all of the patients, irrespective of ganglion size. After 18 months to five years of follow-up, favorable treatment results were observed in 18 patients (90%). In the two remaining patients, in whom recurrences were observed, good results were obtained after repeat aspiration and tetracycline injection [21].

Dogo et al. used hypertonic salt solution and 1% xylocaine in a 2 : 1 ratio to treat wrist ganglions. After ganglion aspiration, 3 mL of this mixture was injected into the cyst. Edema of the wrist and dorsum of the hand was observed in 50% of the patients shortly after the procedure; in most of the cases it resolved within 72 h. Pain was present in 20% of the patients, with peak

intensity within the initial two hours after injection. Only one recurrence was detected after a follow-up of a minimum of one year [23].

## Discussion

When analyzing the issue of administering various chemical substances in the treatment of ganglions of the hand and wrist, several aspects need to be addressed. Firstly, one may get the impression that the choice of chemical substances is somewhat random and inconsistent. The list of substances used in clinical practice includes enzymes, steroids, antibiotics, anesthetics, sclerosants, alcohols and phenols [1–4, 6–8, 10, 13–15, 17, 22, 23], which are medications characterized by very diverse and sometimes even contradictory mechanisms of action. The anti-inflammatory effect of prednisolone is exerted through inhibition of phospholipase A<sub>2</sub> activity and suppression of the release of arachidonic acid, which in turn leads to limited synthesis of inflammatory mediators. The use of steroids in the treatment of ganglions of the hand and wrist is based on the false assumption that the inflammatory process is an underlying cause of ganglion cyst formation [1]. Other substances used in clinical practice are supposed to cause local inflammation and result in the scarring of a ganglion. The effectiveness of this approach is limited, however, due to ganglion wall structure. The wall of a ganglion is composed of collagen fibers organized in layers, with a small quantity of cells (fibroblasts, mesenchymal cells) between them [1, 3]. Since the ganglion wall is almost acellular, its potential to release inflammatory mediators is very limited [1]. It is also worth noting that as pseudocysts, ganglions lack internal cellular lining [3]. The use of sclerosants in the treatment of venous system pathologies is aimed at disintegrating the endothelium and causing endothelial inflammation. These substances cause edema of endothelial cells, which ruptures their cytoplasmic membranes and activates blood platelets, leading to the formation of a thrombus inside a blood vessel [1, 3, 18, 19]. Given the lack of internal cellular lining, the effectiveness of sclerosants in the treatment of ganglions is limited [1].

Secondly, the fact that ganglion aspiration followed by an injection of a chemical substance can be performed on an ambulatory basis is considered advantageous. However, the use of the substances described above is associated with the risk of local and/or systemic complications. Local adverse effects can result from both the properties of a given chemical substance and an incorrect injection technique. Many authors have proposed specific injection techniques to minimize the risk of injecting the chemical substance in an inappropriate location [10, 15, 17].

Limpaphayom and Wilairatana, like Chatterjee et al. [10, 15], employed the technique that most of the



authors used: ganglion aspiration followed by injection of a chemical substance with the use of a single needle and two syringes. Paramhans et al. [17] modified this technique: two needles were inserted in the cyst, opposite each other; one was used to aspirate the fluid from the cyst and then removed, and the chemical substance was injected through the other needle in a volume comparable to the volume of the ganglion. It is worth noting, however, that neither of these techniques precludes the possibility of rupturing the very thin ganglion wall or leakage of the chemical substance at the injection site. When highly irritant substances are used (e.g. alcohol, phenol, sodium tetradecyl sulfate), leakage can lead to serious local complications [20, 22]. Incorrect techniques may result in injecting the substance into a tendon, a joint or a blood vessel. The risk of this last complication is higher in cases of ganglions located on the volar surface of the wrist, since such ganglion cysts are usually adjacent to the radial or ulnar artery [1–3]. Injections in this location are associated with the risk of introducing the substance into the artery, which in extreme cases may lead to distal limb ischemia. When the procedure is performed on ganglions located on the ulnar side of the volar surface of the wrist, the ulnar

nerve is at risk of both mechanical and chemical damage. Similarly, the superficial radial nerve may be damaged during aspiration and chemical substance injection in the treatment of ganglions located on the dorsal aspect of the wrist [1, 3, 24].

Lastly, it should also be noted that the rate of recurrence after aspiration followed by injections of a chemical substance is not low [8–10, 14, 15, 25]. The procedure itself is associated with certain risk of complications. In the opinion of the present authors, ganglion aspiration followed by injections of a chemical substance should be performed by medical practitioners with adequate experience in surgical treatment of ganglion cysts and extensive knowledge of the topographic anatomy of the hand and wrist. Almost 50% of ganglion cysts located in this region have a tendency to resolve spontaneously within several years of observation [1–4]. Taking these factors into consideration, the present authors recommend observation in cases of asymptomatic ganglions of the hand and wrist, and surgical treatment in cases when symptoms such as pain, restriction of limb mobility and weakening of handgrip strength are observed.

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