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Deepika Sondh

M. pharm, Department of
 Quality Assurance, Delhi
 Pharmaceutical Sciences
 Research University,
 (DPSRU/DIPSAR) Delhi, India

Amrita Parle

Associate Professor, Department
 of Quality Assurance,
 Department of Quality
 Assurance, Delhi Pharmaceutical
 Sciences Research University,
 (DPSRU/DIPSAR) Delhi, India

Anti-wrinkle agents - A way of regaining beauty

Deepika Sondh and Amrita Parle

Abstract

Recent development in the technology has led to the advancement in skin cosmetology. Anti-wrinkle or anti-aging agents are extensively used in the cosmetic products, for acquiring a youthful, firm skin. Skin aging is a natural phenomenon which cannot be reversed but with the help of novel approaches in the cosmetology techniques, scientist can delay the process of ageing. Anti-wrinkle agents are used topically for the treating wrinkles and signs of aging. Hyaluronic acid and botulinum neuro-toxins are most the extensively used anti-wrinkle agents. This review article provides the concise details about the leading anti-wrinkle agents, their mechanism of action, uses and adverse reactions on the body. Hyaluronic acid and botulinum neuro-toxins are discussed in detail along with cost considerations. The future trends in the advancement of dermatological aesthetics and anti-wrinkles agents have also been included.

Keywords: Hyaluronic acid, Sodium hyaluronate, Botulinum neuro-toxins, Aesthetics, Dermal injection.

1. Introduction

The Skin

For better understanding of the mechanism of different dermal fillers and anti-wrinkle agents it is important to understand the different layers of the skin. The skin is continuous membrane along with the mucous membranes lining the body's surface. The integumentary system is formed by the skin and its derivative structures (see Figure 1-1). The skin is composed of three layers: the epidermis, the dermis and subcutaneous tissue [1].

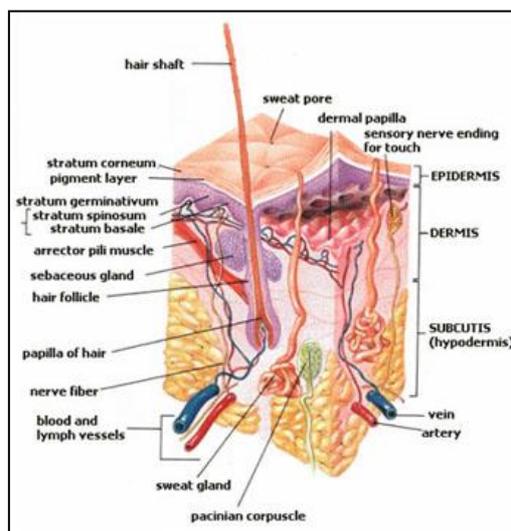


Fig 1: Representation of cross-section of the skin

Epidermis

The peripheral level, the epidermis, comprises of a particular interstellar grouping of cells known as keratinocytes, which synthesizes keratin, a long, threadlike protein with a protective role. The thickness of the epidermis fluctuates in various sorts of skin; it is just 0.05 mm thick on the eyelids, and is 1.5 mm thick on the palms and the soles of the feet. The epidermis contains the melanocytes (the cells in which melanoma builds up), the Langerhans cells (involved in the immune system in the skin), Merkel cells and sensory nerves. The epidermis layer itself is comprised of five sublayers that cooperate to consistently rebuild the surface of the skin [1].

Correspondence

Deepika Sondh

M. pharm, Department of
 Quality Assurance, Delhi
 Pharmaceutical Sciences
 Research University,
 (DPSRU/DIPSAR) Delhi, India

1. Basal Cell Layer
2. The Squamous Cell Layer
3. The Stratum Granulosum and the Stratum Lucidum

Dermis

The center layer, the dermis, is essentially made up of the fibrillary auxiliary protein known as collagen. The dermis is situated underneath the epidermis and is the thickest of the three layers of the skin (1.5 to 4 mm thick), making up roughly 90 percent of the thickness of the skin. The main functions of the dermis are to regulate temperature and to supply the epidermis with nutrient-saturated blood. Much of the body's water supply is stored within the dermis. This layer contains the vast majority of the skins' specific cells and structures, including veins, lymph vessels, hair follicles, sweat organs, sebaceous organs, nerve endings, collagen and elastin.^[1]

The dermis layer is comprised of two sub layers:

1. The Papillary Layer- the upper, papillary layer, contains a thin arrangement of collagen fibers. The papillary layer supplies nutrients to select layers of the epidermis and regulates temperature.
2. The Reticular Layer- The lower, reticular layer, is thicker and made of thick collagen fibers that are arranged in parallel to the surface of the skin. The reticular layer is

denser than the papillary dermis, and it strengthens the skin, providing structure and elasticity.

Hypodermis

The sub cutis is the deepest layer of the skin and comprises of a system of fat and collagen cells. The sub cutis is otherwise called the hypodermis or subcutaneous layer, and capacities as both a separator, rationing the body's warmth, and as a safeguard, securing the internal organs. It additionally stores fat as a vitality save for the body. The veins, nerves, lymph vessels, and hair follicles likewise cross through this layer. The thickness of the sub cutis layer varies all through the body and from individual to individual.

Skin Aging

The hallmark of the aging face is loss of subcutaneous volume over the period of time. Clinically, with this loss, one commonly finds the signs, most clinicians see routinely, when confronted with a patient concerned with the aging face indicated by, an increase in facial vasculature and pigment alterations, as well as an increase in the lines and wrinkles of the skin. This is associated with a thinning of the epidermis \and with dermal atrophy and loss of the elastic tissues present within the dermis and with actinic changes with loss of dermal collagen^[2, 3]

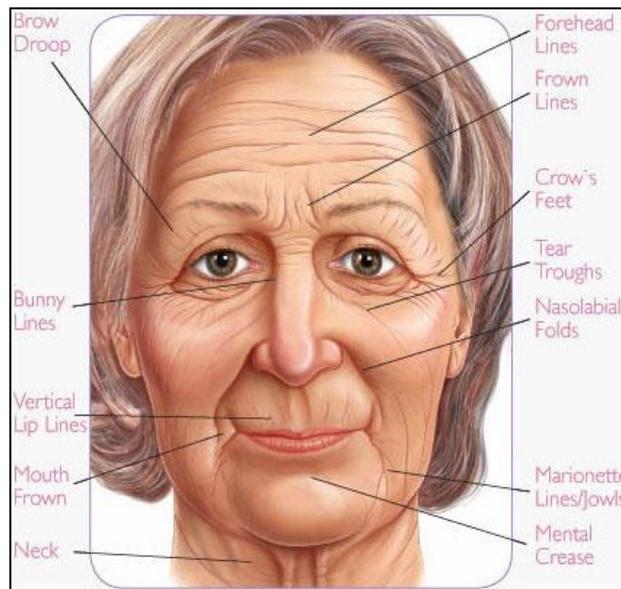


Fig 2: portraying the distinctive locales of the skin having wrinkles

Aging is the procedure of aggregation of molecular damages (NOVOSELTEV et.al 2001)^[2, 3] in organs and life forms, over a time frame, causing loss of some of the prerogative characteristics of youth. Harms are only substance alterations of the cell DNA particles in a living being. Gathered molecular damages in cellular DNA are called substantial changes. As indicated by the gene, where these transformations happen, the physiology of the cell or of the organ changes astoundingly or drastically. Without a doubt, these harms are the ones straightforwardly connected to the obvious sign of the onset of the maturing procedure. The amassing of harms ensuing to the basal metabolism prompts to division of aging into two structures-

1. Natural or Intrinsic Aging- This must be seen in very

seniority and is described by unblemished, smooth, pale, drier, less flexible skin with fine wrinkles. It happens inside the tissue itself, through diminishment in dermal pole cells, fibroblasts, collagen generation and straightening of dermal-epidermal intersection.

For better comprehension of the skin maturing process Paolo U. Giacomoni et.al provoked a model known as- Micro inflammatory model of skin aging. One of the prominent reason for skin aging is diapedesis, the passage of blood cells through the intact capillary walls causing micro inflammation. Diapedesis happens accordingly of anoxia or because of chemotatic signs like introduction to perpetual UVA and UVB, tobacco smoke, electric field and so on. Diapedesis happens by means of Intercellular Adhesion Molecule 1

which is a protein that is encoded by the ICAM1 gene. This gene encodes a cell surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system. Upon synthesis of the ICAM1 gene in the endothelium, circulant monocytes and macrophages roll over and secrete hydrogen peroxide to perform diapedesis across the endothelial lining of the vascular wall. Once in the dermis, the immune cells secrete lythic enzymes and reactive oxygen species (ROS), to fray a path in the dermis. Macrophages in the dermis tend to release collagenases which lead to hydrolysis of collagen. Macrophages also release ROS which damage the nearby resident cells, such as fibroblasts or

keratinocytes. When this happens, the damage can trigger the breakdown of cascade of arachidonic acid and secrete prostaglandins and leukotrienes, which diffuse to the adjacent resident mast cells. Upon binding these mediators on specific receptors, the resident mast cells release histamine and TNF- α , which in turn stimulate the release of *p*-selectins and the neo-synthesis of ICAM-1 in endothelial cells. The cycle is then continued and the micro-inflammatory status is maintained, leading to skin aging [2, 3].

Fig.3, (Giacomoni *et al.*, 2000), summarizes the micro-inflammatory model of skin aging

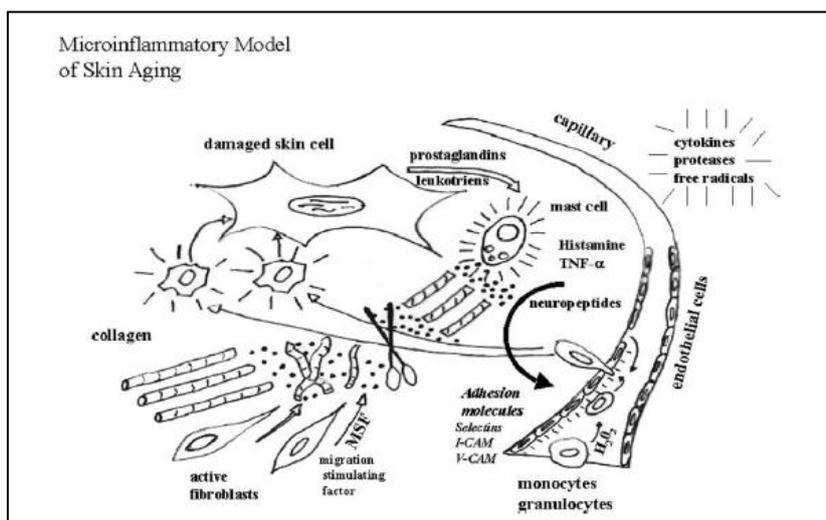


Fig 3: micro inflammatory model of skin aging (I-CAM 1 synthesis) (ref. a mechanistic model for the aging of human skin by Paolo U.Giacomoni, Glen Rein)

1. Photoaging or Extrinsic Aging– It is associated with changes in skin structure and appearance. The greatest source of extrinsic aging is accumulation of chemotactic factor like solar radiation, gravitational attraction, infections, electric fields, psychological stress, cigarette smoke, anoxia and unprotected sun exposure (i.e. photo aging). This is largely confined to the face, neck, hands. Over 80% of facial skin aging is due to low grade chronic UV exposure. Some of characteristics include coarse wrinkles, rough texture, sallow complexion, mottled

pigmentation and loss of skin elasticity [1,2].

Anti-Wrinkle Agents

The treatments for damaged skin range from skin care products, to energy based therapies (lasers, light sources, and radiofrequency devices) to fillers and toxins. Past several years have seen growth in number of new soft tissue augmentation products which are used by physicians in the treatment of aging.

Table 1: List of various anti-wrinkle agents available in the market

No.	Name	Type	Route of administration/ dose	Duration	Effects	Side-effects	Commercialized product
1	Phytoceramide [4]	Herbal agent	<ul style="list-style-type: none"> Topical application depending on severity 	8 days	Increases the depletion of procollagen-1 and fibrillin rich microfibrils in aged skin.	No visible side-effects. But may show allergic reactions in few patients	Bella.vei
2	Hyaluronic acid [5]	Natural chemical	<ul style="list-style-type: none"> Topical application Depending on type of formulation 	12 weeks	It improves tissues hydration and their resistance to mechanical damage	Skin swelling, redness and itching.	Zyderm, Zyplast Cosmoderm
3	Green tea polyphenols [4]	Herbal agent	<ul style="list-style-type: none"> Topical application Varies according to severity 	2-3 months	Decreases the number of langerhans cells and reduce DNA damage in the skin.	No visible side effects.	Antioxidant
4	Garlic extract (cafein acid, S-	Herbal agents	<ul style="list-style-type: none"> Topical application 	1 month	inhibits the degradation of type I procollagen and	Cause skin redness in some patients.	Antioxidants

	allyl cysteine, and uracil ^[6]		<ul style="list-style-type: none"> Depending on severity 		the expressions of MMIPs		
5	Retinol ^[4]	Vitamin-A	<ul style="list-style-type: none"> Topical application 5% concentration 	2-3 weeks	Induce biosynthesis of collagen and reduce expression of MMPI (collagenase)	skin irritation is common	antioxidants
6	Niaciamide ^[4]	Vitamin-B3	<ul style="list-style-type: none"> Topical application 5% concentration 	1 month	regulates cell metabolism and regeneration	No visible side effects.	Antioxidant
7	Tocopherol ^[4]	Vitamin-E	<ul style="list-style-type: none"> Topical application 5% concentration 	12 weeks	Increases the ability of stratum corneum.	No visible side effects	Antioxidant
8	l-ascorbic acid ^[4]	Vitamin-C	<ul style="list-style-type: none"> Topical application 5% concentration 	2-3 weeks	helps build collagen, reduce inflammation, promotes elasticity to plump up skin	No visible side effects	Antioxidant
9	Nifedipine ^[4]	Synthetic chemical	<ul style="list-style-type: none"> Topical application Varies with patients 	30 days	improves the elasticity of the skin, improves the skin pigmentation	Contraindication with steroidal creams. Hypersensitivity reactions	Antioxidant
10	Alpha-hydroxy acid ^[4]	Chemical agent	<ul style="list-style-type: none"> Topical application not more than 8% concentration 	30 days	exfoliators that gently dissolve the "glue" that holds surface skin cells together,	Causes skin redness. Make skin more sensitive in presence of sun light.	Antioxidant
11	Palmitoyl peptide ^[5]	Polypeptide	<ul style="list-style-type: none"> Topical application 	30 days	stimulate collagen synthesis and activate dermal metabolism	Cause skin irritation or redness in some patients.	Polypeptides
12	Botulinum toxins ^[7]	Synthetic chemical	<ul style="list-style-type: none"> Dermal injections Varies with the type of neurotoxins used 	12 months	Botulinum toxin acts at the level of the neuromuscular plate and of other cholinergic synapses	Skin sensitivity reactions may occur in some patients	Botox Cosmetic-Vistabel, Vistabex
13	Chemical peels ^[8]	Synthetic chemicals	<ul style="list-style-type: none"> Topical administration Varies with the type chemicals used 	5-6 months	increase in collagen fibre content water in the dermis has been reported improvement in skin elasticity	Dryness and scaling of the skin	Alpha/beta lipo hydroxy acid, TCE
14	Laser techniques ^[9]	Laser emitting light as 532, 595, 755nm wavelength.	<ul style="list-style-type: none"> Topical administration Varies with the wavelength 	12-16 months	Stimulate fibroblast activity and initiation of tissue repair, enhanced collagen and elastin neoformation	May cause redness, burning of the skin	IPL, LASER

NOVEL TECHNIQUES

15	Adipose derived stem cells. ^[10]	Human dermal fibroblast.	<ul style="list-style-type: none"> Dermal injections Varies with the patients. 	On clinical trials*	Reduces UVB induced apoptosis and stimulating collagen synthesis of human dermal fibroblast.	No visible side effects seen till now.	On clinical trials*
16	Mixture of panax ginseng and crataegus pinnatifida ^[11]	Human dermal fibroblast.	<ul style="list-style-type: none"> Dermal injections Varies with the severity 	On clinical trials*	inhibiting wrinkle formation and increasing moisture in the human skin	No visible side effects seen till now.	On clinical trials*
17	Activation of TGF-β/SMAD and P38 MAPK signaling pathway ^[12]	Dermal multipotent stem cells.	<ul style="list-style-type: none"> Dermal fillers Varies with the patients 	On clinical trials*	activating TGF-β/SMAD and P38 MAPK signaling pathway and then stimulating fibroblast to secrete and synthesize collagen	No visible side effects seen till now.	On clinical trials*
18	DHEA (Dihydro-Piandrosterone) ^[13]	Chemical agent	<ul style="list-style-type: none"> Topical administration 	On clinical trials*	DHEA is steroid hormone involved in physiological aging.	No visible side effects seen till now.	On clinical trials*

			<ul style="list-style-type: none"> • Depends on patient 				
19	Gene silencing ^[14]	Chemical agent	<ul style="list-style-type: none"> • Dermal injections • Varies with the patients 	On clinical trials*	DNA demethylation agents and histone deacylation inhibitors genes	No visible side effects seen till now	On clinical trials*
20	Paracrine cytokine linkage ^[15]	PCL between keratinocytes and fibroblasts	<ul style="list-style-type: none"> • Dermal injections • Depending on the severity 	On clinical trials*	keratinocytes and fibroblasts leads to the stimulation of elastase which helps in maintaining the elasticity and firmness of the skin	No visible side effects seen till now	On clinical trials*
21	Quercetin ^[16]	Herbal agent	<ul style="list-style-type: none"> • Topical administration • Varies with the patient 	On clinical trials*	quercetin caprylate act as a proteasome activator with antioxidant properties	No visible side effects seen till now	Antioxidants
22	Rice-wine ^[17]	Cultured in human fibroblast and keratinocytes	<ul style="list-style-type: none"> • Topical application • No fixed dose 	On clinical trials*	reduces the expression of UV induced matrix metalloproteinase-se-	No visible side effects seen till now	On clinical trials*
23	Pogostone ^[18]	Chemical constituent of patchouli oil	<ul style="list-style-type: none"> • Topical application • No fixed dose 	On clinical trials*	Inhibited the wrinkle formation and skin laxity mainly by repairing collagen and elastic fiber.	No visible side effects seen till now	On clinical trials*
24	Mesenchymal stem cells ^[19]	Medium from human bone marrow	<ul style="list-style-type: none"> • Dermal injections • No fixed dose 	On clinical trials*	Reduces matrix metalloproteinase-1 expression and increased procollagen synthesis	No visible side effects seen till now	On clinical trials*
25	Cyclopia ^[8]	Fermented and non-fermented	<ul style="list-style-type: none"> • Topical application • 2-5% concentration 	On clinical trials*	inhibiting thickening of the epidermal layer, in addition to suppressing collagen tissue breakdown reactions	No visible side effects seen till now	On clinical trials*
26	Coca pod extract ^[14]	Herbal agent	<ul style="list-style-type: none"> • Topical application • Not more than 5% concentration 	On clinical trials*	good antioxidant activity because of phenolic composition and tyrosinase inhibitory activities	No visible side effects seen till now	Anti-oxidants
27	Mixture of human growth factor and hyaluronic acid serum ^[20]	Semi-synthetic	<ul style="list-style-type: none"> • Topical application • Varies with the patients. 	On clinical trials*	HGF and HA serum beneficial in reducing peri orbital Wrinkles	No visible side effects seen till now	On clinical trials*
28	Retinyl retinoate ^[15]	Micro sphere	<ul style="list-style-type: none"> • Topical application • No fixed dose 	On clinical trials*	enhances skin permeation	No visible side effects seen till now	On clinical trials*
29	Autologous platelet rich plasma ^[11]	Whole blood plasma	<ul style="list-style-type: none"> • Dermal injection • No fixed dose 	On clinical trials*	synthesis of collagen and other matrix component by stimulating the activation of fibroblast	No visible side effects seen till now	On clinical trials*

We Will Discuss In Detail the Frequently Used Anti-Wrinkle Agents Namely Hyaluronic Acid and Botulinum Neurotoxins

Hylauronic Acid

Hylauronic acid (HA) has a place with a gathering of substances called mucopolysaccharides having a place with the glycosaminoglycans (GAGs) family. It is a biopolymer made out of repeating units of disaccharides, which incorporate particles of D-glucuronic acid and N-acetylglucosamine atoms connected by β -(1-4) and β -(1-3) glycosides. The human body measuring 70 kg contains 15 g of HA. The best measure of the compound is available in the skin (about portion of the aggregate HA). It can likewise be

found in the spots where rubbing happens: the joints, ligaments, sheaths, pleura and the pericardium. Preparations containing high molecular mass HA can be utilized as a part of arrangements for the care of the eyes, face, neck, and body, and also, in against cellulite, and hostile to extend check beauty care products by framing a defensive layer making skin seem gentler and feel smoother to the touch. The sodium salt of Hylauronic acid is likewise utilized topically to diminishing wrinkles^[21].

Sodium hyaluronate (KH) is currently the most commonly used cosmetic filler. The function of which is to fill and plump up the extracellular tissue space. In liquid formulations, it is utilized to fill little, shallow wrinkles,

giving the skin versatility and adaptability, while cross-connected arrangements are utilized for the adjustment of facial forms, displaying the bosom in ladies. Superb impacts can be accomplished with the redress of nasolabial folds, relieving level brow wrinkles, raising eyebrows, situating the nose, changing the shape and volume of the lips, displaying the cheeks, button, body molding (amplification and demonstrating of breasts, thighs, rump, and calves) and also to improve the state of the labia (labi-aplasty). Little volumes of HA are infused intradermal or subcutaneously to give around

6 months of fill impact. The medication stores likewise offer many creams and oral plans containing KH however so far no randomized reviews have affirmed a positive, long haul smoothing impact on skin wrinkles utilizing these strategies [21].

The cost of different products containing hyaluronic acid is given in the table no.2. The treatment varies according the factors like the severity of the wrinkles, age of the patient and the units injected to the patient and the outcome may last up to 3-6 months depending on the same factors [22].

Table 2: Products Containing Hylauronic Acid

Product	Component	Company	Units	Cost(Inr)
Hyaluronic Acid Gel	Hyaluronate sodium	Meso System S.A	30g	2,560
Oz Naturals hyaluronic acid serum	Retinol, Hyaluronic acid, vitE	Oz Naturals	30ml	2,373
Hyaluronic acid serum	Hyaluronic acid, vit E	Cosmedica	15ml	1,892
Hylauronic acid serum	Hylauronic acid, retinol	Pyrochem pvt ltd	30ml	700
Hylauronic acid cream	Hylauronic acid, vit E	Macaria cosmetic	30g	300
Hylauronic acid (2%)	Pure hyaluronic acid	Cosderma pvt ltd	15ml	2,500
Synvisc one injection	Hyaluronic acid	Archit biotech	10ml	1200

Botulinum Neuro-Toxins

Botulinum neurotoxin is the exotoxin produced by Clostridium botulinum. Seven distinct serotypes of the neurotoxin, designated as type A to G, have been identified. Type A is the most commonly used toxin for cosmetic purposes, although there are some reports about the use of type B toxin in aesthetics. The toxin is a protein molecule consisting of a 50-kd light chain and a 100-kd heavy chain linked by a disulfide bond. [24]

At present, there are four ordinarily utilized arrangements of botulinum toxins [25]-

- Ona-botulinum toxin A (Botox; Botox Cosmetic, Allergan, Irvine, CA),
- Abo-botulinum toxin A (Dysport; Ipsen Ltd Berkshire, UK),
- Inco-botulinum toxin A (Xeomin; Merz Pharmaceuticals, Frankfurt, Germany),
- Rima-botulinum toxin B (Myobloc; Solstice Neurosciences, San Francisco, CA).

Despite the fact that the clinical impact of each is comparable, they contrast in their synthetic structure, related proteins, assembling and refinement forms and clinical viability.

Dosage, Duration and Storage -The normal dosage of the botox infusion relies on upon the seriousness, mark name, length and in addition recurrence of the treatment. The

measurements depend on the biologic intensity of the toxin and is measured in units. A 100-U vial of the preparation contains 5 mg of toxin as lyophilized powder. Since the arrangement is in powder form, it should be reconstituted before the infusion. The prescribed diluents are 0.9% saline without additives. It is typically prescribed to tenderly infuse the diluents into the vial, staying away from the arrangement of froth in the perplexing, which could bring about toxin denaturation. Once reconstituted, the arrangement must store at a temperature of 2°C to 8°C. After reconstitution, the arrangement ought to be utilized within 4 hours. The cost of the treatment changes relying on the seriousness of the wrinkles, age of the patient and the units infused to the patient, and the result may last up to 6-8 months relying upon the same factors [25], the cost of various items is given in the table no.3

Common indications of botulinum neurotoxin are brief change in the presence of direct to serious glabellar lines, the treatment of brow lines, crow's feet, bunny lines, upper and lower perioral lip lines, gingival grin, doll lines, dimpled button, vertical neck lines [23, 24].

Complication- Overcorrection, Under correction, Asymmetric result Upper-eyelid ptosis, Dysphagia, neck shortcoming, Perioral hang, Bruising, Globe aperture, Diplopia (horizontal rectus), Psychosomatic problems [26,27].

Table 3: List of Commercially Available Botox Injections

Product	Company	Units	Cost/Unit(Inr/Usd)
Botox cosmetic	Allergan, Irvine, California	50ml	1650/120
Dysport	Ipsen Ltd Berkshire, UK	50ml	1780/290
Xeomin	Merz-Pharmaceuticals, Frankfurt, Germany,	50ml	1050/230
Myobloc	Solstice-Neurosciences, San Francisco, CA	50ml	1,050/230
Neurobloc	Solstice Neurosciences Inc, San Francisco, California	50ml	700/125
Botox injection	P&R Export	50ml	1000
Botox injection	Plasma life care	100ml	1800
Botox powder	Fanatic pharma	50ml	5000

Conclusion

The above comprehensive study about the types of anti-wrinkle agents summarizes the current modalities available in aesthetics for treating the signs of aging. Hyaluronic acid may

show hypersensitivity reactions in some patients. The clinically accepted and most frequently used anti-wrinkle agents includes hyaluronic acid which is used in different type of topical preparation for treating early sign of aging, whereas

botulinum neurotoxin is used as Botox injections and administrated intra-dermally in the skin for the treatment of wrinkles in the different parts of the body. The article also throws light on the ongoing clinical trials using future novel techniques for the treatments of wrinkles and other facial deformities. Addition of antioxidants such as niaciamide, tocopherol, green-tea polyphenols etc. to the topical preparations of hyaluronic acid probably further wrinkling of the skin have no clinical side effects on the skin and body when applied topically.

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