Nat. Volatiles & Essent. Oils, 2021; 8(4): 15990-15999

NVEO
Natural Volatiles &
Essential Oils

Effectiveness Of Angioprotector Sulodexide For The Correction Of Vascular Complications In Children With Secondary And Residual Palatal Deformities After Uranoplasty

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Abstract

In this article, authors discussed efficiency of angioprotector substance -sulodexidein the correction of vascular complications in pediatric patients with secondary and residual palatal deformities after uranoplasty.Sulodexideshowed its anticoagulant effect in the experiments and clinical trials.Moreover,it has an antithrombotic effect, which it implements mainly through the mechanisms of suppressing the activity of the internal and external pathways of prothrombinase formation. Activation of fibrinolysis cause of Sulodexide was investigated and confirmed, thereby improving local microcirculation has also identified. It restores the structure and functional integrity of the endothelium, reducing the number of desquamated endothelial cells in the peripheral blood, thereby increasing its antithrombogenicity and thromboresistance.

Keywords: Sulodexide; uranoplasty; vascular complications; congenital clefts; angioprotector effect; fibrinolysis.

INTRODUCTION

Treatment of patients with congenital cleft of the upper lip and palate (CCULP), accompanied by dento-alveolar anomalies and deformities of the nose, is one of the most difficult tasks of modern dentistry and maxillofacial surgery. The provision of qualified assistance to this group of patients provides for multi-stage surgical interventions, constant dispensary observation and treatment by a number of specialists, surgeons, orthodontists, speech therapists, pediatricians, otorhinolaryngologists, etc.

In the complex rehabilitation of patients with CCULP, the leading place is given to surgical treatment (AA Mamedov, 2002, LV Kharkov et al, 2005, BN Davydov, 2006, MZ Dusmukhamedov, 2006; V Y Hoffman, 2006). The methods of surgical treatment are always in the center of attention of maxillofacial surgeons, the results of patients' treatment are constantly improving. In our opinion, it is hardly possible to find a section of surgery that, in terms of the number of proposed methods of surgical intervention, surpassed the surgical treatment of congenital clefts of the face.

Along with the great advances in surgery of the Congenital clefts of the upper lip and palate, the results of surgical interventions do not completely satisfy both patients, their parents, and surgeons. Most authors believe that none of the modern methods of primary uranoplasty can completely restore characteristic anatomical and functional disorders and prevent the development of secondary deformities (Toirov U.T., 1989; Kozin I.A., 1996; Bessonov S.N., 2005 ; Sykes JM, 2007). After carrying out various types and techniques of uranoplasty, secondary (SD) (postoperative) and residual defects (RD) often occur, which can be located in the region of the anterior, middle and other parts of the hard palate, on the border of the hard and soft palate or the soft palate. The variety of clinical manifestations of SD and RD of the palate and factors influencing their occurrence, duration and difficulties of treatment, instability of results make it urgent and necessary to further study their pathogenesis and improve treatment methods.

The modern literature indicates the positive effect of low molecular weight heparinoids on the state of the antithrombotic potential of the endothelium of microvessels and the process of fibrinolysis that underlie vascular lesions. When tissue is damaged, the blood vessels are destroyed and their contents are released. Blood clot formation restores homeostasis and provides a temporary matrix for cell migration. In this case, platelets not only participate in the formation of a clot, but also secrete various growth factors and mediators. The process of wound healing is also associated with the influx of leukocytes - neutrophils, macrophages, lymphocytes, as well as mast cells - into the wound focus. After surgery, an inflammatory process is stimulated in the wound, which leads to an increase in the production of pro-inflammatory cytokines IL-1a and P, TNF-a and IL-6, which enhances the adhesion of leukocytes to endothelial cells and facilitates their transmigration across the endothelial barrier. violation of the ability of macrophages to phagocytose dead cells. Recent scientific studies have shown that the absence of macrophages in the inflammatory or proliferative phase of healing leads to a decrease in the formation of granulation tissue in the wound and the inability to proceed to the next phase of healing. The proliferation stage is characterized by an influx of fibroblasts, deposition of ECM, and the formation of new blood vessels. New blood vessels develop from existing vessels (angiogenesis). At the same time, angiogenic factors are secreted by fibroblasts, macrophages and endothelial cells themselves. Therefore, postoperative wound healing depends on macrophages and the state of the main homeostatic systems. Prolonged hypoxia caused by insufficient perfusion and insufficient angiogenesis is the main factor leading to impaired wound healing. To heal postoperative wounds, blood flow to the site of injury is required. Insufficient supply of blood, enriched with oxygen and nutrients to the wound, leads to a delay in the healing process. The better the blood supply to the tissues around the wound, the more active its healing is. With a complete or partial absence of blood flow, cell hypoxia occurs, and it goes over to anaerobic metabolism. The work of the potassium-sodium pump is also disrupted, which is accompanied by an increase in the intake of sodium and calcium through the cell membrane, an increase in intracellular osmotic pressure, inducing edema. Free oxygen radicals formed during tissue reperfusion are capable of affecting all biological

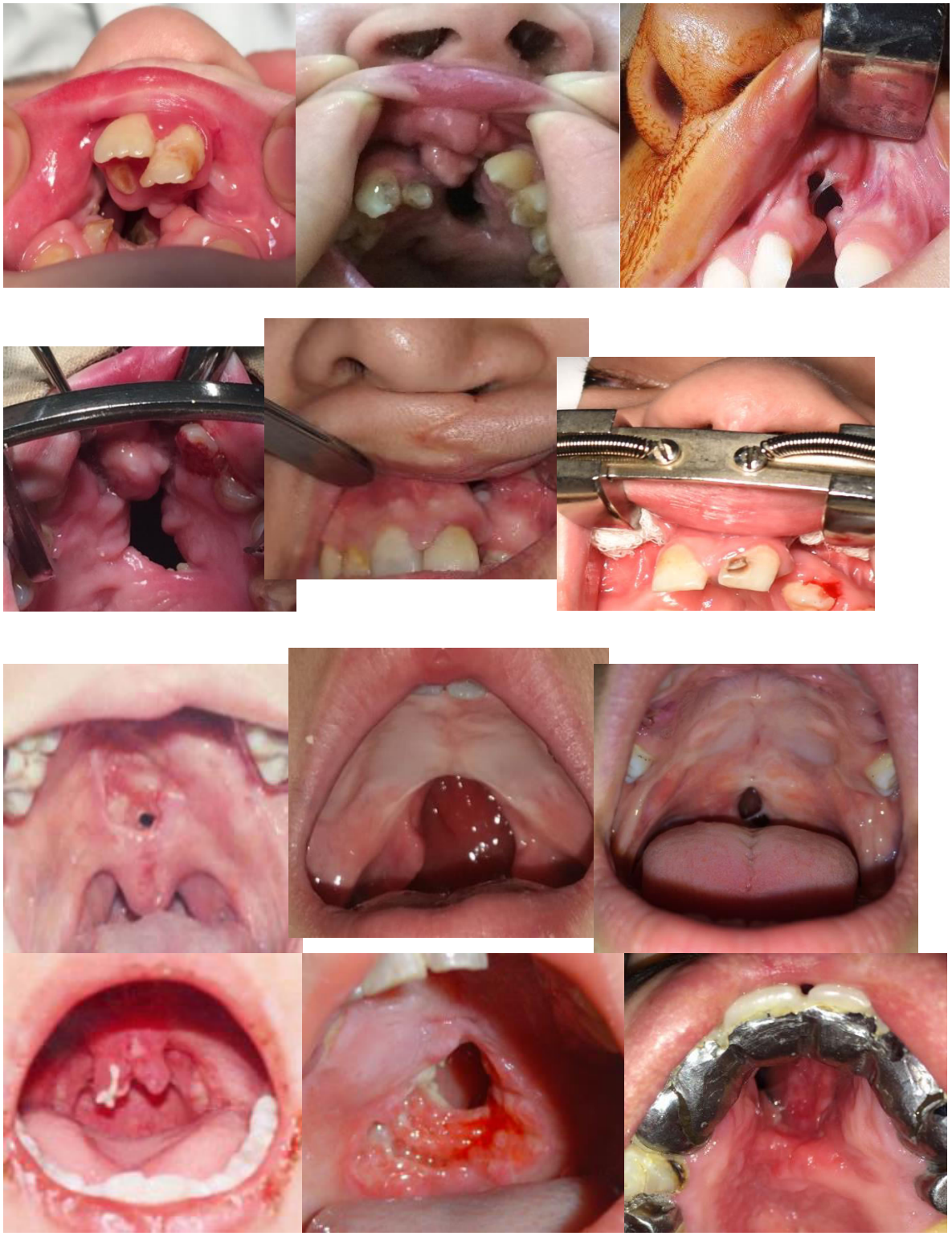
substances, contributing to the degradation of the endothelial collagen layer and basement membrane. This leads to microthrombosis and an increase in the permeability of the vascular wall, which is the cause of the development interstitial edema. Thus, the most important factors that increase the risk of cicatricial hypertrophy are decreased microcirculation and tissue hypoxia. In the modern literature there is evidence of the positive effect of low molecular weight heparinoids on the state of the antithrombotic potential of the endothelium of microvessels, on the rheological properties of blood and fibrinolysis underlying vascular lesions. The foregoing determines the need for a comprehensive study of the state of vascular complications and their role in the development of secondary and residual palatal deformities after uranoplasty in children in order to optimize the treatment tactics of patients.

The aim of this study was to study the efficacy of the angioprotectorsulodexide for the correction of vascular complications in children with secondary and residual palatal deformities after uranoplasty.

MATERIAL AND RESEARCH METHODS

To clarify the frequency, localization and mechanisms of the development of secondary and residual palate defects in connection with the use of various uranoplasty techniques, we studied 47 archival case histories of children with Congenital clefts of the upper lip and palate who were treated in the department of pediatric surgical dentistry of the Andijan regional hospital in the period from 2010-2019. and the department of pediatric maxillofacial surgery in the clinic of the Tashkent State Dental Institute in the period from 2010-2019. To systematize the residual and secondary defects and deformities of the upper lip, alveolar ridge and palate, the classification of E.N. Samara (1977, 1981), where the author identifies the following forms: defects of hard, hard and soft, soft, connected defects. In terms of size, defects can be: small (up to 1 cm), medium (up to 2 cm), large (more than 2 cm).

As you know, the results of uranoplasty largely depend on the completeness of the restoration of the anatomy of the palate and in the correct position of the pathologically altered muscles of the soft palate, which ensure the otopharyngeal closure. Our retrospective analysis of the case histories of patients with secondary (SD) and residual defects (RD) of the palate in children with Congenital clefts of the upper lip and palate shows that they have a peculiar clinical picture. The clinical picture of SD and RD of the palate after uranoplasty largely depends on the shape of the cleft and the method of uranoplasty, while SD and RD of the palate have the most common favorite localizations: they were located along the former cleft, had a different shape and size - from 3 to 22 mm. The most common complication of uranoplasty is the discrepancy of the sutures (SD) at the border of the hard and soft palate 18.5%. SD of this localization, as a rule, develops due to the anatomical features of the cleft and technical errors of the operation (Pic. 1)



Pic. 1. forms and localization of SD and RD after uranoplasty

The results of a retrospective analysis of case histories showed that 41 (87.2%) patients in the preoperative period had a severe somatic background - as prescribed by the pediatrician, they received antianemic treatment for several months, often received anti-inflammatory drug therapy and were somewhat lagging behind in physical development from their peers. The present study was aimed at studying the state of vascular complications and their role in the development of secondary and residual palatal deformities after uranoplasty in children in order to optimize treatment tactics

for patients. To solve this problem, we studied the possibility of using low-molecular tenarinoid-sulodexide to correct changes in the microcirculatory link of the hemostasis system in children with secondary and residual deformity of the palate after uranoplasty. To do this, we selected patients after diagnosis and divided them into the following groups: the comparison group (n=14) consisted of children with SD and RD of the palate before uranoplasty, who received traditional treatment (n=13); the main group children with SD and RD of the palate before uranoplasty received sulodexide according to the following scheme: 300-600 LSU intramuscularly once a day for 2 weeks; control group (n = 14) children without pathology of the dentoalveolar system. All studies were conducted with informed consent. All patients who participated in the study were examined by a doctor and underwent clinical, laboratory and instrumental studies upon admission to the hospital. Blood sampling for the study was carried out in the morning, on an empty stomach, by gravity into a plastic test tube. A detailed study of the hemostatic system was carried out, which included the determination of the number of platelets in the peripheral blood, the resistance of capillaries, the number of desquamated endothelial cells (DEC) in the blood according to the method of J. Hladovec (1978) to assess the degree of damage to the vascular wall, activated partial thromboplastin time (APTT) , prothrombin ratio (PR), prothrombin index (PTI), thrombin time (TT), fibrinogen level, time of XIIa-dependent fibrinolysis, content of D-dimers and soluble fibrin-monomeric complexes (SFMC). All research methods used are described in the monograph by Barkagana Z.S. (2001). Determination of the level of endothelin-I, vasculoendothelial growth factor in blood serum was carried out by enzyme-linked immunosorbent assay using a kit of reagents from “БиоХимМак” (Russia). Statistical processing of the results obtained was carried out on a personal computer with the operating system Windows 10 using software packages Excel 2010; statistical multifunctional program Statistica V.6.0. using basic methods of parametric and non-parametric statistics. To assess the reliability of the revealed differences, the Student's t-test was used with a statistically significant border of $p < 0.05$.

RESEARCH RESULTS AND THEIR DISCUSSION

Comparison of the indicators of the hemostasis system in the preoperative period in patients of the comparison groups and the main group with the data of the control group showed that fibrinolysis was suppressed in all patients, soluble fibrin-monomeric complexes and desquamated endothelial cells circulate in the blood in increased quantities. In addition, in patients of the main group, the activity of the factors of the prothrombin complex is somewhat reduced. When comparing coagulograms of patients in both groups, the differences relate only to the lower activity of the prothrombin complex factors and the higher number of desquamated endothelial cells in the main group compared with the comparison group. Probably, the revealed differences in the number of desquamated endothelial cells are associated with the fact that among the patients of the main group there were more persons with concomitant pathology, systemically affecting the vascular endothelium and accompanied by damage to the endothelial lining, the marker of which is a change in the content of circulating desquamated endothelial cells in the blood (5 , 29). Under the influence of conventional therapy in patients of the comparison group, the activity of factors of the external mechanism of prothrombinase formation decreased (an increase in the prothrombin ratio and a decrease in the value of the prothrombin index). Despite antithrombotic prophylaxis, an increase in the level of fibrinogen in the blood was observed in patients of this group, while the antithrombin activity of the blood (an increase in thrombin time) and fibrinolysis increased. It should be noted that in the postoperative period there was a quantitative increase in the content of soluble fibrin-

monomeric complexes and D-dimers in the blood, indicating the degradation of fibrinogen and fibrin during their enhanced proteolysis by thrombin and plasmin. Surgical aggression led to an increase in the number of circulating desquamated endothelial cells.

Table 1. Parameters of the hemostasis system in the control, comparison and study groups

Indicators of the hemostasis system	Control Group (n=14)	Comparisongroup (n=14)	The main Group (n=13)
Partially activated thromboplastin time (sec).	29,78±1,54	31,58±2,81	34,83±3,17
Prothrombinindexin (%)	100,58±9,13	103,69±8,64	98,15 ±7,94
Fibrinogen, (g / l)	3,24±0,27	4,21±0,38	3,31±0,29
Thrombintime (sec)	15,37±1,25	22,08±1,54	15,68±1,43
XIIa-dependent fibrinolysis, min	7,24±0,64	8,13±0,79	14,32±1,17
Soluble fibrin monomeric complexes (g / l $10^{-2)}$	4,02±0,02	6,71±0,48	3,31±0,27
Д-димеры, мкг/мл	0,33±0,02	0,61±0,04	0,31±0,02
Desquamated endothelial cells (cells / 100µl)	2,34±0,21	4,41±0,37	2,21±0,16
thrombocytes, -x10^9/ l	232,18±9,51	174.23±11,9	257,18±13.7
Endothelin -1 (µMol / L)	1,98 ± 0,21	3,02 ± 0,25	1,34± 0,12
Vasculoendothelial factor growth rate (VEGF) (ng / ml)	0,92±0,08	1,64±0,13	0,98±0,09

Note: * - reliability of differences P <0.05 relative to the control group

The results obtained indicate that conventional therapy was mediated through inhibition of the external mechanism of prothrombinase formation, increased antithrombin and fibrinolytic activity of the blood. At the same time, this therapy was unable to protect endothelial cells from their further damage, in patients of the comparison group.

In contrast to the conventional therapy, sulodexide in patients of the main group, along with the external mechanism of prothrombinase formation, caused lengthening of APTT, while the level of fibrinogen in the blood did not significantly change during the entire observation, being at the level of control values. Sulodexide influenced the antithrombin activity of blood plasma, i.e. progressively activated its fibrinolytic activity. It also contributed to the reduction of soluble fibrin-monomeric complexes in the blood and the number of desquamated endothelial cells in it. Thus, sulodexide implements its antithrombotic effect mainly through the mechanisms of suppression of the activity of the internal and external pathways of prothrombinase formation, activation of fibrinolysis and protection of endothelial cells.

Comparison of the indicators of the two studied groups of patients in the postoperative period gave grounds to emphasize the most significant mechanisms of the antithrombotic efficacy of

sulodexide. At the same time, sulodexide is more effective, inhibits the activity of factors of the internal and external mechanisms of prothrombinase formation, which, most likely, inhibits the formation of the protein of the acute phase of fibrinogen in patients in the immediate postoperative period. In addition, sulodexide clearly activates XIIa-dependent fibrinolysis, which is one of the factors inhibiting the conversion of fibrinogen to fibrin. Finally, sulodexide has an angioprotective effect, protecting endothelial cells from damage. Perhaps, due to the indicated properties of sulodexide, we did not observe episodes of postoperative microcirculation disorders in patients of the main group. Our experience showed that when using sulodexide, no postoperative hemocoagulation complications (large and small bleeding, disseminated intravascular coagulation) were detected. The drug, while maintaining the coagulation mechanism, ensures the prevention of disorders in the microcirculation, which is especially important in patients with its damaging effect on vascular endothelial cells.

As is known, vascular growth factors are endogenous regulators of angiogenesis. The study of the content of vascular endothelial growth factor (VEGF) in the blood serum makes it possible to assess the violation of the formation of the vasculature, the most important factor of repair, without which physiological wound healing is impossible. The obtained research results, as indicated in our previous studies, the dynamics of the vasculoendothelial growth factor indicator in children with secondary and residual defects and deformities of the palate after uranoplasty showed an increase in the studied indicator, which indicated the risk of developing hypertrophic scars. Since the main source of VEGF and the main target of its action are vascular endothelial cells, and with the development of their dysfunction, an imbalance of all processes in which these cells take part occurs. When using sulodexide, the studied indicator approached the values of the control group. The next task of our study was to study the factors influencing endothelial dysfunction, in particular, endothelin-1. Endothelin-1 - along with the ability to modulate the tone of the vascular wall, has the properties of a growth factor, stimulating the proliferation of mesangial cells, vascular smooth muscle cells, fibroblasts and endothelial cells. There is evidence that endothelin plays an important role in oxidative stress and cell apoptosis. The analysis of the obtained results of the study presented in Table 1 indicates a significant increase in the level of endothelin-1 in the blood serum in the examined children with secondary and residual defects and deformities of the palate after uranoplasty with conventional therapy, while the indicators of the main group were within the control values.

Thus, correction of the coagulation link of plasma hemostasis in sick children with secondary and residual defects and deformities of the palate after uranoplasty showed a violation in the hemostasis system, which indicates the need to study the state of the vascular wall at the time of surgery and after it. If violations are detected in the indicators of vascular-platelet and fibrinolytic links of the hemostasis system in the preoperative period, it is necessary to include in the arsenal of therapy the drug with a complex effect on the vascular wall and coagulation hemostasis.

CONCLUSIONS

Sulodexide, has an anticoagulant effect, and also has an antithrombotic effect, which it implements mainly through the mechanisms of suppressing the activity of the internal and external pathways of prothrombinase formation. Sulodexide also significantly activates fibrinolysis, thereby improving the state of local microcirculation. And finally, it restores the structure and functional integrity of the

endothelium, reducing the number of desquamated endothelial cells in the peripheral blood, thereby increasing its antithrombogenicity and thromboresistance.

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