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HYPERTROPHIC SCARS AND KELOIDS: A RECURRENT PROBLEM REVISITED

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SUMMARY

Excess scarring caused by pathologically overabundant collagen deposition is a problem known by all surgeons. Such complications to wound healing known as hypertrophic scars and keloids might turn out aesthetically unacceptable to the patient and some scars might even cause anatomic dysfunction.

Reviewing the literature in planning a strategy of treatment the surgeon encounters an overwhelming amount of hypotheses on the topic. There seems to be no absolutely effective treatment for hypertrophic scars and keloids and the number of treatment modalities illustrate the lack of understanding concerning this kind of pathologic scarhealing. Most studies have not been well controlled and have produced conflicting results.

This review outlines the nature of hypertrophic scars and keloid. Based on a critical assessment of current treatment modalities some guidelines for the choice of treatment is proposed.

ZUSAMMENFASSUNG

Die hypertrophischen Narben und Keloiden: die Revision des zurückkomendes Problems

V. Ellitsgaard, N. Ellitsgaard

Übermässige Narbenbildung durch pathologisch üppige Kollagendepositionen ist ein Problem, das jedem Chirurgen bekannt ist. Solche Komplikationen bei der Wundheilung, bekannt als hypertrophische Narben und Keloiden, können für den Patienten aus ästhetischen Gründen unakzeptabel sein und manche Narben können sogar anatomische Dysfunktion verursachen. Beim Durchgang der Literatur zur Planung einer Behandlungsstrategie stösst der Chirurge auf eine grosse Menge von Hypothesen zu diesem Thema. Es sieht jedoch so aus, als ob es keine absolut effektive Behandlung der hypertrophischen Narben und Keloiden gibt, und die Menge der Behandlungsmöglichkeiten illustriert den Mangel an Kenntnis von dieser Art patologischer Narbenbildung. Die meisten Studien wurden nicht gut kontrolliert, was widersprüchliche Ergebnisse brachte.

Diese Übersicht befasst sich mit der Natur der hypertrophischen Narben und Keloiden. Auf Grundlage einer kritischen Bewertung der aktuellen Behandlungsmöglichkeiten gibt es weiterhin Vorschläge für Richtlinien bei der Therapiewahl.

Key words: keloid, hypertrophic scar, wound healing

Hypertrophic scars and keloids are pathological excess scarring following skin injury. They may occur even after the most technically correct surgical procedure and many humans experience the occurrence of a hypertrophic scar even though it may be small, transient, and does not produce a serious problem. Some injuries do, however, cause massive hypertrophic scars and, in some cases, keloids, both of which in addition to their cosmetic significance, can promote anatomic dysfunction when involving one of the body joints.

In such cases where treatment is desirable, knowledge of the two types of excess scarring, their individual behaviour and prognosis is of great importance to the strategy of treatment. A critical appraisal of the literature is however difficult because most reports are retrospective and hence inherently biased and many publications include patients without specifying the type of scar pathology.

The classical feature of the keloid is that the scar tissue progressively invades surrounding normal skin whereas a hypertrophic scar, however large it may become, is confined to the tissue damaged by the original injury and increases in bulk by pushing out its margins and not by invasion. Both lesions are characterised by overabundant collagen deposition (1, 2). This differentiation has never been challenged, yet in practice it is often ignored.

Epidemiology

Keloid is seen exclusively in humans. It occur in all races, with a preponderance of the lesions in darker-skinned races, the incidence up to 15 times higher than in whites (3). The male-to-female ratio is approximately equal and the prevalence of keloid probably lower than that of hypertrophic scar, but no definitive figures are known (4). The frequency of occurrence of keloids has been reported to be higher during the second and third decade of life (5). According to Muir keloids never occur before puberty, whereas hypertrophic scars may develop at any time during life (2). Patients who form hypertrophic scars and keloids as children or teenagers may not exhibit this tendency in later life (6).

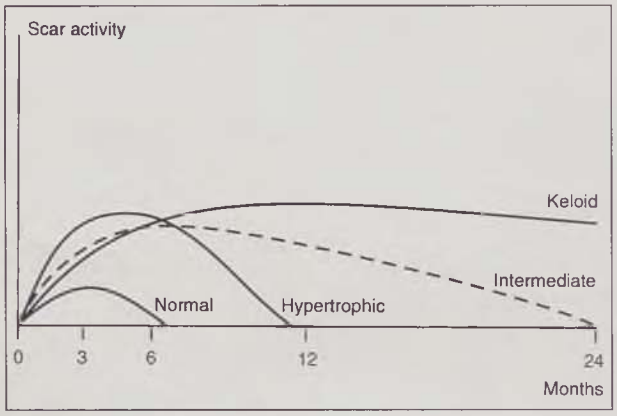

Fig. 1: Activity of different types of scars in relation to time. Reproduced from Muir, I. F. K. On the nature of keloid and hypertrophic scars. Br. J. Plast. Surg., 43: 61-69, 1990. Reproduced with the permission of the author and of the Editor, British Journal of Plastic Surgery.

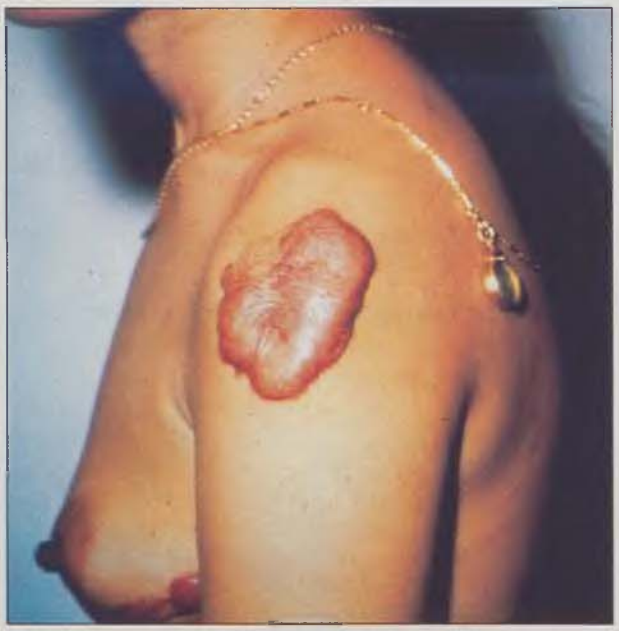

Fig. 2: An example of keloid formation after vaccination in a female of indian origin. Note that scar formation is rampant and extends far beyond the confines of the original wound.

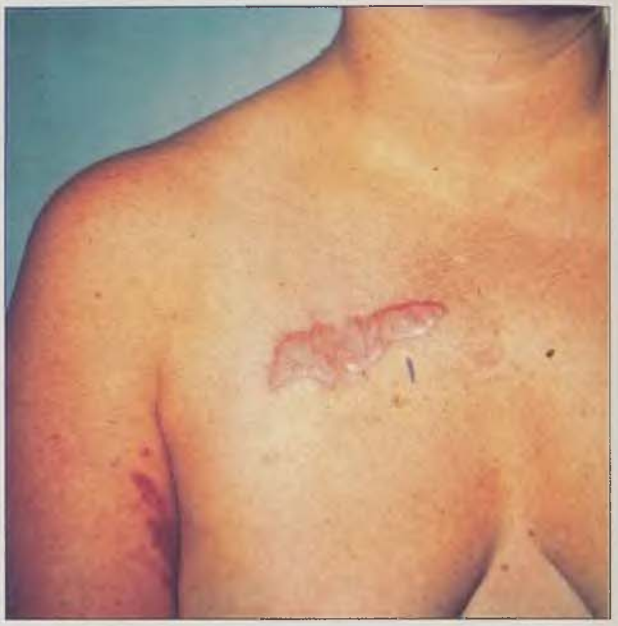

Fig. 3: An example of hypertrophic scar formation after excision of a naevus. Note that scar formation is excessive, yet located within the borders of the original wound.

Clinical features

As several studies on scar tissue show, a differentiation between the two lesions is often impossible as a result of a single clinical examination only. The hypertrophic reaction might be so intense that a hypertrophic scar is incorrectly regarded as a keloid, thus rendering the choice of treatment difficult. A different approach can then be made by studying the evolution of the activity of scars in relation to time, see fig. 1 (2). The activity is assessed on the grounds of itchiness, redness and increase in size. The scars are measured and photographed. If patients are seen at intervals over some years and then reviewed retrospectively, it becomes clear that excessive scars fall into 2 major groups according to the time scale of activity. Further confirmation that such a grouping is valid comes from the way in which other factors -age, anatomical distribution, presence or abscense of initiating factors, and longterm evidence of invasion -correlate with the different patterns of activity (2). Hypertrophic scars follow an obvious skin injury (surgical incisions, burns or scalds). The scars become erythemateous and irritable and increase in size quite rapidly for three up to six months. The condition then remains static for some months, after which regression commences. The redness and irritability decline first, decrease in bulk and softening occurring much more slowly. These scars may occur after skin trauma in any part of the body and at any age although there is a maximum intensity in children aged 6 - 7 years. These scars do not invade normal tissue, they do not increase after 6 months and therefore, no matter how

great the intensity they should all be designated as hypertrophic scars.

In keloids, the intensity of reaction is usually less than in the above mentioned hypertrophic scars but activity continues for many years and long-term observation shows evidence of spread into the surrounding normal skin. This persistent activity is a feature of young adults and not infrequently the lesions are multiple. The anatomical distribution of these scars seems to some extent to be related to skin-colour. In white-skinned people the most susceptible region is the presternal area and with diminishing frequency keloids are seen over the front of the chest, the back and the shoulders. In persons of African negro origin and in some Asians (7, 8) the area of keloid occurence is similar however somewhat wider, extending into the neck, lower face and onto the upper arms.

In some ways excessive scars in the deltoid region and in ears (after earlobe piercing) behave in a different, less clearcut manner. In these regions an age relation and duration of activity somewhat dissimilar to the above mentioned grouping makes differentiation more difficult (2). Differential diagnostically allergic contact dermatitis secondary to earrings might produce keloid like lesions on the earlobes. Studies of such lesiòn show however a dense infiltration of lymphoid cells and the formation of lymphoid follicles (9, 10).

Histology

The histologic differentiation between keloids and hypertrophic scars has been subject to much discussion and some confusion.

Blackburn and Cosman (11) differentiated keloids from hypertrophic scars on the basis that keloids appeared to contain bundles of collagen with focal proliferation or nodules and increased quantities of mucopolysaccharides. Hunt (12) found that hypertrophic scars contained nodules, (whorls), keloids did not. Knapp et al. (13) suggested that the nodules demonstrated collagen with a random architecture. Linares et al. (14) found nodules in both, but never in mature scars. Later Kischer et al. (15, 16) reviewed the literature and reported on several original studies in which both keloids and hypertrophic scars show a highly organized connective tissue unit in the form of multiple collagenous almost avascular nodules of different sizes surrounded by sections of microvessels. The nodules are elongated, cigar-shaped bodies virtually always orientated parallel to each other, to the skin surface and with their long axis parallel to the lines of flexion-extension of the underlying musculature (16).

Using the scanning electron microscope they found that on a submicroscopic level there is however a repeatable difference. In normal skin the collagen bundles are distinct, of 8 to 10 mmmm in diameter, running parallel to the epithelial surface, randomly connected to each other by fine fibrillar strands of collagen or elastin (cross-linking). In a hypertrophic scar the collagen bundles are flatter and less clearly demarcated, their fibres being loosely arrayed in a wavy pattern, fragmented and shortened. The majority of bundles are still lying parallel to the epithelial surface. The ultrastructure of keloids are even less organized, discrete collagen bundles almost do not exist and the collagen fibres form haphazardly connected, loose sheets that appear randomly oriented to the epithelial surface. The fibrils are larger and more irregular, and the interfibrillar distance is less than that in hypertrophic scars (17). Both lesions have a predominant active fibroblast cell type containing vast arrays of rough endoplasmatic reticulum and Golgi membranes. Both lesions show myofibroblasts derived from resident fibroblasts (18), the relative frequency of which is controversial (17, 19).

In 1982 Kischer et al. (20, 21) compared the microvasculature of keloid and hypertrophic scars with that of normal dermis and normal scar. They observed an increased occlusion of the microvessels by endothelial cell proliferation in the abnormal scars and proposed the below mentioned hypoxiaselectivity hypothesis.

Hypotheses on etiology

According to Kischer (22) hypertrophic scars and keloids are inevitably the results of surface injuries. Despite the many and varied theories as to their origin, no qualitative or special factor has been identified to account for their development (20, 4). It is possible that a biomechanical defect responsible for abnormal scar formation is expressed early in the course of wound repair, too early to be detected by the time abnormal lesions are fully developed. Unfortunately, there are no studies on early formation of keloids to test such a hypothesis.

Collagen production is elevated in keloid biopsies and in cultured fibroblasts derived from keloids (23). No significant differences in DNA content or cellularity has been observed in keloids compared with normal dermis (11, 24), suggesting that each fibroblast within a keloid is producing excessive collagen, as opposed to an increased number of fibroblasts each producing a normal amount of collagen. It may be that excessive collagen-producing fibroblasts are selected by the wound environment and that this selection results in excessive collagen production in the lesions. Several studies support this theory. In 1978 Hunt et al. reported that increased hypoxia is seen in early animal wounds and that hypoxia stimulates macrophages, in turn, to stimulate fibroblast collagen production (25). This event is now known to take place in humans too (26). According to Kischer et al. (20, 21) the above mentioned microvascular occlusion in hypertrophic scar and keloids creates a hypoxic environment in these lesions. Moreover, increased lactate, increased histamine (27, 28) and decreased pH following hypoxia are characteristics of hypertrophic

scars and keloids that conceivably could create a „stressed" environment selecting fibroblasts that are high collagen producers, and known to be facultative anaerobes and metabolize adequately, or are stimulated, in low oxygen environments (12).

The hypoxia-selectivity hypothesis is substantiated by reports (29, 30) demonstrating that heterogenous populations of fibroblasts with particular biomechanical characteristics can be isolated from normal tissue. Perhaps certain kinds of fibroblasts predominate in abnormal scarring and either (a) fail to respond to regulatory signals ending increased collagen production during early wound healing or (b) are selected and proliferate more abundantly in the „stressed" environment of the early wound. There is evidence that keloid-derived fibroblasts isolated in vitro are a selected subset of normal dermal fibroblasts that occur more abundantly in abnormal scars. Such fibroblasts produce increased extracellular matrix components in vitro (24, 23, 31), and demonstrate a differential response to hydrocortisone (32) and histamine (32, 33) compared with normal fibroblasts. According to Russell et al. (34) the keloid derived fibroblasts have reduced growth factor requirements. However, such „abnormal" cells are morphologically identical to normal fibroblasts and grow at the same rate (24). Further studies are required to verify the hypothesis that abnormal scars result from a population of normal dermal cells preferentially selected during wound healing. Keloids and hypertrophic scars may result not only from increased collagen production but also from a relatively decreased collagen degradation. Several authors including McCoy et al. (35, 23) have shown that collagenase activity in excess scarring is greater than in mature scars and normal skin. A tenfold increased activity in keloids is shown, in spite of which a disproportionate increase in collagen synthesis leads to deposition of excess scar.

Diegelmann et al. (36) described the presence of the plasma proteins aaa-1-antitrypsin and aaa-2-macroglobulin in the interstitial space of abnormal scars. Elevated levels of such collagenase inhibitors might influence the effect of collagenase and contribute to a lack of collagen degradation (20, 37). Another reason for decreased collagen degradation might be an overabundance of chondroitin-4-sulphate (15), which makes collagen fibres resistent to digestion by collagenase (38). Also an immunological basis for excess scarring has been sought. Some authors have shown delayed hypersensitivity reactions to cutaneous antigens, such as sebum, melanin and blood products. Antigens to antinuclear antibodies directed against fibroblasts have been found (39). Cohen et al. (40) found increased levels of IgG and Bloch et al. (41) found IgM and C3 to be increased, while IgA and C4 were normal. Epidermal growth factor is seen in increased amounts in keloids and normal scars. The addition of transforming growth factor-beta retards normal scar growth, but not keloid growth, suggesting that growth factor plays a regulatory role in formation of keloids (39, 40, 41). Cohen analyzed the HLA profiles of keloid and non-keloid formers and found no significant differences in the incidence of HLA A and B antigens (40).

A higher fibronectin concentration is found in hypertrophic scars and keloid compared with normal dermis (31, 22). Fibronectin is usually very abundant in wounds between the first 24 and 48 hours of injury and then gradually disappears. The persistence of fibronectin in excess scarring may be regarded as an indication of „prolonged wound healing" which in turn may account for the prolonged activity of fibroblasts (42).

The addition of hydrocortisone or triamcinolone acetonide to fibroblast cultures has been shown to retard their growth, inhibit the activity of prolyl hydroxylase and reduce the synthesis of collagen (43, 32, 35, 44). When keloid-derived fibroblasts were compared with normal dermal fibroblasts, collagen synthesis was however less inhibited by hydrocortisone in the keloid-derived fibroblast line. This suggests that the defect in wound healing that results in keloid formation is associated with a change in a regulatory mechanism that controls the rate of collagen synthesis and is sensitive to physiological levels of hydrocortisone (44, 45).

Finally a mechanical theory of keloid development should be mentioned. In normal wound repair the tensile strength is increased during the maturation phase by cross-linking of the collagen fibrils and realignment of fibres along tension lines, the process may be reinforced by a slight traction applied from the surroundings as the patient starts mobilizing (12). In case of increased tension on the wound edges, the tension is transmitted to fibroblasts, which respond with excess collagen formation (46, 6, 47, 48). Increased tension is noted normally in certain anatomical locations like the sternum and deltoid regions, and it can be iatrogenically induced by excising a large tumor or by crossing relaxed skin tension lines. A patient with normal scar formation in tension-free areas may form abnormal scars in skin under tension. In one study, often quoted, excised keloid, grafted onto an area of relatively little tension, was found to atrophy (49); however, this occurrence may have involved factors others than tension. The tension-theory does not explain why scar release does not always cure keloids and why the earlobe is such a susceptible area.

Treatment modalities

Several forms of treatment have been utilized for keloids and hypertrophic scars, with varying degrees of success. Results of different studies evaluating similar methods do not always agree and no treatment regimen has been universally succesful on repeated evaluations. Searching for a treatment to be recommended one encounters the fact that very few studies will withstand critical

evaluation. Several studies have been performed without distinguishing between keloids and hypertrophic scars whose natural history is that of spontaneous regression. Because of problems with differentiation others simply treated all excessive scarring as a keloid. Most studies are retrospective evaluations of methods in which criteria differs widely from study to study. There are few comparative studies of various treatment methods and very few randomized prospective studies with long-term follow-up. The definition of treatment response and recurrence are frequently not well defined.

Excision

Excision is beneficial only when used in conjunction with pharmacologic and/or pressure treatment to prevent the inevitable recurrence of keloids after excision alone. Smaller lesions usually are treated without surgery, while large lesions may require surgical debulking prior to the use of other modalities (4). Intending to relieve tension after surgery, one solution is excision and skin grafting. A full-thickness graft is preferred as a primarily closed donor site has a lower incidence of abnormal scar formation than a split-thickness donor site (50). Some authors have recommended to limit the excision leaving a rim of scar, the so-called intralesional incision (1, 51), which may be followed by either depot steroid (triamcinolone) injections (52) or perioperative radiotherapy (53, 54). There are however no solid data to support this concept (55). Insertion of a tissue expander several months before excision followed by „tension-free" wound closure (56) does not prevent recurrence of the keloid (55).

An alternative way of excision is performed by laser, which has the advantages of simultaneous hemostasis and minimal tissue necrosis.

Using the carbon dioxide laser a high recurrence rate is seen (57), for which reason Stucker et al. combined the excision with a meticulous follow-up using injections of triamcinolone acetonid and hyaluronidase. A succes-rate of 80% was however depreciated by the lack of control group and problems with patient compliance (3). The Nd: YAG laser might reveal somewhat better results, but follow-up has till now been inadequate (58, 59). Cryotherapy has been used on keloids with some success in open, uncontrolled studies (60, 61). The therapeutic effects of cryotherapy depend on direct cell damage as well as microcirculatory changes leading to cell necrosis. After two to ten treatment sessions of two or three freeze-thaw cycles complete flattening was seen in 60 - 70% of keloids younger than two years. A somewhat higher responce rate in clinical scar hypertrophy may be due to spontaneous regression. At follow up median 25 and 32 months respectively (60, 61) no recurrence was seen in scars that initially responded well to the treatment. Atrophy and hypopigmentation of the skin are inevitable with this treatment. A combined use of cryotherapy and intralesional steroid injections has been reported giving similar results (56).

Radiotherapy

The rationale of radiation therapy is to destroy the fibroblasts responsible for the excess collagen formation. If enough fibroblasts are destroyed a balance between collagen synthesis and degradation will be created. A significant drawback to its use is however that radiation nonselectively destroys collagen-producing fibroblasts in the lesion as well as in surrounding connective tissue (55). Radiotherapy in the form of superficial X-ray therapy (62) or treatment with Strontium 90 beta rays have found widespread use during the century. As the results of radiation alone is cosmetically inferior to surgery and radiation combined (65) most studies report on radiation as an adjuvant to excision (5). Preoperative radiation in combination with postoperative treatment does not offer advantages (66, 67). Enhamre and Hammar (54) treated keloids with postoperative radiotherapy and followed them up from 6 months to 9 years. Using a total dose of 1200 rads (cGy) they had a cure rate of 88%, and found that single or fractionated doses and time interval between excision and irradiation did not influence the result. Other studies report on a similar success in preventing recurrence using doses of 1500 cGy post surgery (68, 53, 66, 67).

The indications for radiation are not well defined. The radiation techniques and response rates vary widely from study to study making comparisons difficult (5) and the lack of randomized prospective studies with long-term follow-up makes radiation difficult to evaluate as a therapeutic method. Recently Norris (69) reviewed 18 studies and outlined a suggested prospective protocol.

Hyperpigmentation is a known side-effect to the treatment, whereas cancer induction is extremely rare (64). Radiation is however known to increase the incidence of malignancy and controlled studies with a follow-up as long as required simply do not exist. For that reason several authors reserve radiotherapy for keloids resistant to any other treatment modalities (37, 70). The fact that some still advocate the use of radiation, even „in children and young people" (64, 67), must be explained in terms of economy, convenience and patients compliance.

Pressure

The use of mechanical pressure in the treatment of excessive scars was first reported by Rayer in 1835. In the late 1960s the use of pressure treatment of hypertrophic scars and keloids and the severe contractures after burn injury became a standard treatment in burn facilities universally (71). Although pressure has been reported by several studies (72) to be an effective therapy both in cases of established keloid and as

a prophylactic measure in burns and after surgery, no study has been able to fully validate the mechanism by which pressure alters scars (73, 74, 75, 76, 77). Baur et al. suggested a metabolic explanation for the effects of pressure. A decreased blood flow to the scar second to pressure might cause decreased delivery of aaa-2-macroglobulin. By reducing the amount available of this collagenase-inhibitor, collagen breakdown progresses (73). Histologically Larson et al., treating postburn hypertrophic scars by pressure, found relatively looser collagen bundles, increased interstitial space, and a decreased number of cells (75). Nodules did not develop during pressure treatment (74). Kischer et al. (76, 77, 78) reports on a reduced level of chondroitin-4-sulfate and a degenerative appearance of endothelial cells and pericytes similar to what is found in older lesions, suggesting that pressure treatment alters the ratio of collagen metabolism so that catabolism becomes dominant. The pressure exerted must exceed the inherent capillary pressure of 24 mmHg (76) and the treatment should be maintained day and night for from 4 to 6 months (6) up to one year or more (73, 79). Problems have been encountered in that when the pressure is removed for any length of time, hypertrophic scarring may occur. Different techniques have been used to produce pressure (71). A succesfull approach to keloids of the earlobe and the pinna has been the use of a clip-on earring (72). The pressure treatment have no major physiologic complications. The long lasting treatment might however cause definite problems with patient compliance.

Steroids

Steroid injections have been a standard treatment for keloids and hypertrofic scars for many years (5). As mentioned above, corticosteroids do not inhibit protein synthesis in keloid-derived fibroblasts. The popularity of topical steroid treatment in keloids may therefore be attributed to the positive effect on collagenase activity by decreasing the concentration of aaa-2-makroglobulin (35). Also the DNA content in lesions treated with steroid is decreased, suggesting that the drug decreases the cellularity of the lesion (80).

Intralesional injections of triamcinolone acetonide in a concentration of 40 mg per ml without local anesthesia is suggested by Peacock and Cohen (55). The lesion should be infiltrated by injection of the steroid into the upper dermis where dispersion is widest (55). Steroid injections alone at six to eight weeks interval will improve but not cure a keloid. The best results are reported after either an intraoperative injection alone (81) or intra-operative injection followed by post-operative injections at monthly intervals, the treatment lasting for 6 to 10 months, with subsequent doses given for recurrence (37, 82). Steroid-impregnated tape, used early, is also useful in managing excess scar formation (83). A major disadvantage of the treatment is however that the reiterated injections are extremely painful despite the use of a local anesthetic and non-compliant patients may be one reason why some studies on this treatment modality show suboptimal results. Side effects of steroids are relatively common and include skin atrophy, depigmentation (reversible) and telangiectasis (84, 85). A systemic response to topical steroids is rare.

Other treatment modalities

The use of silicone gel was introduced fourteen years ago in the treatment of burn scar hypertrophy, where it was found to soften and reduce scars faster than pressure therapy (86). During the eighties several uncontrolled clinical reports stated that topical silicone gel sheets promote resolution of hypertrophic scars (87, 88, 89). Another study, also uncontrolled, suggest that true keloids also regress after treatment with topical silicone gel (90). In a study including observations on untreated adjacent control scar in each patient, Ahn et al. (91) studied the effects of a silicone gel sheet on the resolution of hypertrophic burn scar and the prevention of hypertrophic scar formation in fresh surgical incision. The sheets were worn for at least 12 hours daily for at least one month. A statistical significant effect was seen on scar elasticity, color and size in both groups. Unfortunately an adequate follow-up is missing. Sproat et al. (92) performed a prospective, randomized trial to compare the standard Kenalog injection of established hypertrophic sternal scars with topical silicone gel sheet worn continously for 12 hours for 12 weeks. Ten out of 11 patients favored the silicone gel treatment which provided an earlier symptomatic relief and a more aestetic scar. Studies have shown (87) that the beneficial effects are not due to pressure, temperature, oxygen tension, or capillary occlusion. Possible mechanisms under investigation are hydration of the stratum corneum and/or release of a low-molecular-weight silicone fluid (92). In two studies Sawada and Sone (93, 94) advocated the former theory after having tested the use of silicone oil in both scar hypertrophy and keloid. Their findings suggested that occlusion and hydration mechanisms were the main basis of the therapeutic action of silicone sheets. Clugston tested silicone-gel sheeting on early wound healing in the hairless guinea pig and found no significant adverse effects on wound strenght (95). Sproat recommends silicone gel sheet as a first choice treatment of especially immature scars due to its painless application and easy care (92).

Other pharmacologic methods which have been tried include among many others: penicillamine, colchicine, betaamino-propionitrile (BAPN), retinoic acid, vitamin E, and intralesional interferon gamma therapy. Penicillamine and colchicine reduce the secretion of collagen from the fibroblasts (96) and enhance collagenase activity (97). BAPN and penicillamine block colla-

gen crosslinking by reducing its initial steps (98). Intralesional interferon gamma therapy is based on a lymphokine which can downregulate collagen synthesis in vitro and in vivo. Intralesionally application of 0.05 mg a week for 10 weeks has resulted in a decreased linear dimension and flattened scars without systemic side-effects (99).

CONCLUSION

Apart from prevention no single therapeutic modality is best and in each case the location and appearance of the lesion, the age of the patient and past response to treatment determine the type of treatment to be used. If there is a question as to whether the lesion is a keloid or a hypertrophic scar the before mentioned criteria should be kept in mind and the lesion observed for 6 months to 1 year to evaluate a possible spontaneous regression.

Considering treatment the surgeon should, at an early stage, ascertain whether the patient's objective is to eradicate the esthetic and/or functional deformity, to prevent recurrence by treatment or whether the aim is merely to ameliorate the physical discomfort and itching. If eradication is wanted, patients must be warned that recurrence is a risk. If the lesion is not aesthetically displeasing, the patient should be advised not to have it excised. In case of burning and itching, control may be possible with intralesional injection of triamcinolone and/or systemic antihistamines (55).

When treatment is needed possible disadvantages must be taken into consideration. The risk of local - or systemic side-effects must be weighed against the demand for treatment and the expected result.

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CARPAL TUNNEL SYNDROME
Revision of the Thenar Motor Branch ?

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SUMMARY

This paper presents the authors' views and experience with operations of carpal tunnel syndrome. Because of the multifactorial etiology of the disease they cannot recommend a schematic solution using a single surgical procedure for the treatment of all patients. During an operation much depends on the local findings as well as on the neurological ones. Individual steps during an operation are analyzed and discussed with regard to their risks and the authors deal also with the asset from the aspect of causality of the approach. The authors recommend revision of the thenar branch of the median nerve.

Between January 1994 and October 1996 the authors investigated 212 patients. EMG examinations were performed prior to surgery in all cases. General evaluations showed favourable postoperative results in 94% of individuals.

ZUSAMMENFASSUNG

Der Syndrom des karpelen Tunnels: die Revision des motorischen Thenar-zweiges.

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Die Autoren präsentieren in ihrer Zusammenfassung ihre Ansichten und Erfahrungen aus den Operationen des Syndroms des karpalen Tunnels (KT). Für die multifaktorale Ethiologie der Erkrankung können sie nicht die schematische Lösung empfehlen, die nur als einziges Operationsverfahren für die Behandlung aller Fälle benutzt wird. Vor allem es ist notwendig, sich bei der Operation mit dem lokalen Fund zu richten, der durch den neurologischen Fund unterstützt wird. Die Analyse der einzelnen Operationsschritte und deren Diskusion wird gerade im Hinblick auf ihre Risiken durchgeführt. Es wird auch der Beitrag aus Sicht der Kausalität diskutiert. Die Autoren empfehlen die Revision des Thenar-zweiges des nervus mediani.

In der Zeitperiode 1/1994 - 10/1996 wurden 212 Fälle beobachtet. Vor der Operation wird bei 100% EMG durchgeführt und in der gesamtem Bewertung wurde bei 94% ein gutes postoperatives Ergebnis gefunden.

Key words: carpal tunnel syndrome, surgery of carpal tunnel syndrome, revision of thenar branch of median nerve

Paget in 1863, and Nothnagel in 1867 described „vasomotor neurosis of the hand". The symptoms they described were later known as carpal tunnel syndrome (1).

In conjunction with the development of this syndrome, in the course of investigations many diseases or general conditions were suspected - rheumatic diseases, tendosynovitis, abnormalities of the wrist, posttraumatic changes, tumours or diabetes mellitus, amyloidosis, pregnancy, climacteric, and menopause.

Typical symptoms associated with carpal tunnel syndrome, accurately diagnosed by clinical examination and EMG are indications for surgery.

SURGICAL PROCEDURE

Individual steps of the operation, from the approach, nerve decompression, synovectomy, revision of the thenar branch, etc. were modified over the years: form broad S shaped approaches and Z shaped incisions to an endoscopic approach. With the selection of the surgical approach views on subsequent steps of the operation naturally also changed. In our opinion a short incision, careful revision of the nerve, epineurotomy or epineurolysis, revision of the thenar branch, in particular its entry into the thenar fascia and indicated excision of the hypertrophic or pathologically altered

synovia of the flexors is the correct method to obtain good results.

The operation is made under local anaesthesia with addition of epinephrine or POR-8. A bloodless method is not used.

The surgical approach should meet the following criteria (4):

1. Overview of the nerve in the entire carpal tunnel bed
2. Possibility to revise the thenar branch
3. Possibility to spare the palmar branch of the median nerve

We consider sufficient an incision which starts approximately in the middle of the palm, follows the linea vitae and ends proximally near the linea rascetta. We do not proceed to the distal forearm, as wounds heal poorly there, are more painful than on the palm and also have a greater tendency of keloid changes. We consider short 1.5 - 2 cm long surgical incisions (5) above the area of the ligamentum carpi transversum as sufficient for access to the nerve and its decompression. However for revision of the thenar motor branch of the median nerve these incisions are not sufficient. We have no personal experience with endoscopic methods. That procedure however is not consistent with our belief that it is necessary to examine and treat the median nerve. Moreover, in the literature complications are reported (incomplete discision of the ligament, arterial, nervous, tendinous injuries; 4, 11) which were not encountered in our groups. According to our experience a 4 cm incision on the palm which ensures a good overview without tissue contusion, heals after 10 days without complications and interfering elements during the subsequent course. After one year it is hardly visible.

After sharp severing of the transverse ligament we make the median nerve accessible. The proximal portion of the ligament and distal part of the antebrachial fascia is severed (after exposing the nerve) with scissors partly under visual control (6).

The subsequent procedure depends strictly on the peroperative finding:

Condition of the nerve: its compression, adhesions, pallor, cyanosis or altered thickness, elasticity and width of the epineurim and condition of the synovia of the flexors can be, after a certain practice with operations in this area, readily evaluated. In the majority of cases epineurotomy is performed and perineural fibrosis is assessed. Epineurotomy makes it possible to evaluate with an unaided eye, magnifying glasses or microscope the quality of the epineurium (thickness, elasticity etc.). A tough inelastic epineurium is not exceptional. It forms a firm compressing nerve sheath and after its resection along the whole circumference the nerve acquires its typical colour. According to our results and observations during surgery we reached the conclusion that this step is appropriate. Statistical investigation revealed a significant agreement between findings of these pathological changes of the epineurium with the loss of sensitivity or muscular hypotrophy (1, 2, 11) upon clinical examination. This certainly increases the chance of development of postoperative adhesions. We assume however that this is only a slight increase as compared with the achieved effect of nerve release. In our group there were some 38% patients with a tough inelastic epineurium which had to be removed. Experimentally this experience was tested (Rydevik, 7) on rabbit nerves, even during endoneurolysis. .We use interfascicular neurolysis (endoneurolysis) only exceptionally in younger patients when the nervous lesion is severe and there is a markedly pathological EMG finding. We do not have much confidence in the regenerating capacity of the nerve in the age bracket when carpal tunnel syndrome is encountered most frequently. Preparation of individual nerve fascicles reveals that they are filiform, hypothrophic, frail and subsequently frequently severely oedematous; during the postoperative period irritation phenomena frequently develop, even if only temporarily. Without this operation their incidence is almost zero and therefore this step must be carefully considered. It is necessary more frequently in operations of relapsing complaints, in cases of adhesions and after incorrect administration of corticoids in conservative treatment. Objective evidence of the necessity of endoneurolysis (e.g. EMG) is lacking. At this point one must decide based on personal experience and the use of magnifying glasses or a surgical microscope.

Subsequently, we proceed in a distal direction towards the insertion of the thenar motor branch of the median nerve. Its exposure and the preparation of its insertion into the thenar fascia is important. This insertion is, according to our experience, another „bottleneck" in about one third of patients, a site of compression of the nerve, the role of which is not negligible in subtle motor activity of the hand. From the results of EMG, nerve compression at this site cannot be reliably confirmed nor ruled out and therefore revision is necessary. Sometimes the anatomical variety of the insertion of the branch of the median nerve is quite surprising. After some practice with these operations its revision is however a question of several minutes and its identification facilitates and hastens possible later synovectomy.

In case of compression in the area where the motor branch passes into the thenar fascia it is not sufficient to dilate the opening by means of Péan froceps or to enlarge by incision. In both instances formation of a scar can cause a relapse of equal or greater compression. If the opening is tough, and narrow, it is essential after discision of the fascia and exposure of the thenar branch to create a defect in the fascia to achieve a wider entry for the nerve. As a rule a triangular defect is made to maintain the patency of the fascia. This step had to be used in approximately one third of the patients.

In addition, during the operation the synoviae of the flexors is also evaluated. When its hypertrophy or pathological condition is suspected, partial synovectomy is performed in the bed of the carpal tunnel. Contrary to workers who always perform synovectomy (8), we hold the view that due to the multifactorial etiology of carpal tunnel syndrome this step does not always respect an individual approach. We decide according to the surgical finding which they check by histological examination after synovectomy. Synovectomies were performed in approximately 20% of the patients, histological examination confirmed a pathological finding in approximately 60%.

After irrigation the wound is closed by an intradermal suture, and a drain is inserted for 24 hours.

OBSERVATIONS AND RESULTS

Carpal tunnel syndrome is a disease which affects mainly women, in our group mostly in the age bracket of 40 - 50 years, with fewer in the 50 - 60 year age bracket. In men the maximum incidence is between 50 and 60 years.

According to case-histories the cause of the disease is in 70% of patients great physical strain, overburdening of the hands and wrists (milk maids, workers operating machines, but also typists and computer operators). It is combined with hormonal changes in approximately 42% (approaching climacteric, menstrual disorders, induced menopause), in approximately 35% thyroid disorders and in 4% injury of the extremities with plaster immobilization.

The duration of the patients complaints, suggesting carpal tunnel syndrome, before operation, is given in Table 1.

Table 1. Duration of carpal tunnel syndrome symptoms before operation

duration	<1 yr.	1 yr.	2 yrs.	5 yrs.	>10 yrs.
% of patients	2	8	30	50	10

Between January 1994 and October 1996 we investigated a total of 212 patients with operations for carpal tunnel syndrome. All patients were indicated for surgery, based on case-history, and clinical and EMG examinations. The results were evaluated as follows:

excellent - elimination of subjective and objective complaints (= EMG)

very good - elimination of subjective complaints and improvement of objective (EMG) parameters

good - improvement of subjective complaints while preoperative neurological defects persist

poor - no improvement

The overall evaluation of results after an operation of the carpal canal in the described manner is presented in Table 2. Table 3 and Table 4 present the results after operations with regard to the electromyographic examination. The clinical and EMG examinations were always made 2 - 3 months after operations. Before operations electromyographic examinations were performed for all patients. After the operations 198 patients (93.3%) were examined by EMG. The group with poor results after operations includes two patients who developed Sudeck's algodystrophy and one patient whose postoperative condition was complicated by infection of the wound. These complications were cured conservatively. The mean period of work incapacity of the patients was 6 - 7 weeks. In 68 patients (32%) it was necessary to modify the entry of the thenar branch of the median nerve into the thenar fascia.

Table 2. Overall evaluation of results after operation of carpal canall (clinical and electromyographic examination)

Result	excellent	very good	good	poor
No. of patients	146	34	19	13
% of patients	69	16	9	6

Table 3. Evaluation of improved sensitive rate of conduction according to electromyographic examination

% improvement according to EMG	100	50	25	not improved
% of patients	76	12	9	9

Table 4. Evaluation of terminal rate of conduction of motor fibres according to electromyographic examination

% improvement according to EMG	100	50	25	not improved
% of patients	55	26	16	9

DISCUSSION AND CONCLUSION

Individual steps were discussed already when the procedure of the operation was described. We present the following conclusions:

- Because the etiology is not quite clear, but mainly because there are more probable factors leading to carpal tunnel syndrome, it is important to have several alternatives in the programme of the operation. The use of a single rigid procedure is not recommended.

- We advocate only two constant steps which lead to the abolition of the „bottleneck" syndrome, i.e. severing of the ligamentum carpi transversum volare and revision of the entry of the thenar branch into the thenar fascia. Although adjust-

ment of the entry into the fascia is necessary only in approximately one third of the patients, from clinical and EMG findings it cannot be predicted when this extension will be necessary. Therefore, we recommend revision of the thenar branch of the median nerve in all instances.

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CHANGES OF CRANIOFACIAL GROWTH AND DEVELOPMENT IN MALES WITH COMPLETE UNILATERAL CLEFT LIP AND PALATE BETWEEN THE AGE OF 5 TO 20 YEARS

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SUMMARY

The study is based on an anthropometric assessment of X-ray films obtained in two series of males with complete unilateral cleft lip and palate. The first series was examined at the age of 5, 10 and 15 years, the second series at 15 and 20 years. The films were assessed with Jarabak's analysis. The aim of our study was to compare the amount of growth and character of developmental changes in the prepubertal, pubertal and postpubertal period of life. The highest growth rate of skeletal structures was present in the prepubertal period, it was somewhat slighter in the pubertal period and it still continued in the postpubertal period. The high growth rate in the prepubertal period was probably related to the eruption of permanent teeth. In spite of a marked deterioration of sagittal jaw relations during the prepubertal period an improvement of an overjet was attained. However during the puberty and the postpubertal period a further improvement was not recorded. The results are in agreement with facial type of growth characterized by a slight pubertal spurt.

ZUSAMMENFASSUNG

Die Veränderungen des kraniofaziallen Wuchses und der Entwicklung bei den Männern mit einem völligen einseitigen Lippen- und Gaumenspalten im Alter von 5 bis 20 Jehren

M. Drahorádová, Ž. Müllerová, Z. Šmahel

Diese Arbeit ist auf der anthropometrischen Bewertung der Teleröntgenaufnahmen von 2 Gruppen der Männer mit dem völligen einseitigen Lippen- und Gaumenspalten gegründet. Die erste Gruppe wurde mit 5, 10 und 15 Jahren untersucht, die andere wurde mit 15 und 20 Jahren untersucht Die Aufnahmen wurden mit Hilfe der Jarabks Analyse bewertet. Das Ziel stellte die Vergleichung der Größe und des Charakters von den Wuchs- und Entwickungsveränderungen in vorpubertaler, pubertaler und postpubertaler Lebensperiode dar. Die Wuchsgeschwindigkeit der Skelettstruktur war in der vorpubertaler Periode die höchste, um ein bißchen weniger war sie in der pubertaler Periode und zum kleineren Teil überdauerte sich auch in der postpubertaler Periode. Die hohe Wuchsgeschwindigkeit in der präpubertaler Periode hängt wahrscheinlich mit Durchbrechung der Zähne des dauerhaften Gebisses zusammen. Auch über die markante Verschlechterung der zwischenkiefrigen Vertical- und Sagittalverhältnisse, zu der in der vorpubertaler Periode kommt, gelang es im Laufe dieser Periode mild den Biß im frontalen Gebiet des Gebisses zu verbessern. Während der Pubertät und in der postpubertaler Periode kam es zu keiner Verbesserung mehr. Die Ergebnisse entsprechen dem faziallem Wuchstyp mit relativ ausdrucklosem pubertalem Spurt.

Key words: unilateral cleft lip and palate, X-ray cephalometry, growth and developmental changes, Jarabak's analysis

The main differences in craniofacial growth and development in patients with clefts were confirmed many times. Subjects with clefts are characterized by a growth deficiency and retrusion of the maxilla, by a shortery ramus and a steeper body of the mandible, an impairment of sagittal and vertical jaw relations, a reduced anterior growth rotation of the lower jaw and a concave facial profile. An impairment of jaw relations leads to unfavourable development in the dental region. A posteriorotation of the mandible could result in an open bite and a deterioration sagittal jaw relations promote the development of an anterior crossbite.

The aim of this study was to describe and assess developmental changes of some linear and angular dimensions in patients in the age from 5 years to adulthood and to compare these changes occurring in prepubertal, pubertal and postpubertal periods. A knowlage of the exact course of

changes and their amount in individual periods allows construction of growth curves of some craniofacial structures and to use them for the comparison of the findings in individual patients and for the evaluation and planing of treatment.

The main advantage of this study is the fact, that it is based on longitudinal data. For the assessment of X-ray films was used the Jarabak's analysis. This method was devised for orthodontic diagnosis, but it represents also the most widely used method for the assessment of patients with clefts.

MATERIAL AND METHOD

The study is based on an assessment of lateral X-ray films of the skull obtained in 55 males with complete unilateral cleft lip and palate (UCLPc) without associated anomalies. We have evaluated 147 X-ray films and subdivided them into two series. The first series consisted of X-ray films in 29 patients at the age of 5 (mean age 5,25), 10 (mean age 10,58) and 15 (mean age 15,08) years and second series consisted of films in 34 patients at the age of 15 (mean age 15,08) years and in adults (mean age 20,17 years). In 8 patients X-ray films were obtained in above mentioned all age groups, therefore they were included into both series. Cheiloplasty according to Tennison was performed at the age of about 7 months. In 20 patients (born in 1966-1968) was carried out simultaneously bone grafting, in 35 patients (born in 1973-1978) was used periosteal flap surgery. Since we did not study the effects of individual methods, each series contained one half of patients with bone grafting and one half of patients with periosteal flap surgery. Palate surgery with a pushback and pharyngeal flap surgery was carried out at a mean age of 4 years in patients with osteoplasty and at the age of 5 years in patients with periosteoplasty.

The X-ray films were obtained under standard conditions during centric occlusion. The head of the patient was fixed in a cephalostat. For an assessment of films was used the Jarabak's method. The craniometric points and reference lines used in this analysis do not correspond to the international cephalometric convention, therefore they are presented in Figure 1. The distance between two points is marked by dash (e.g. N-S), the perpendicular distance of a point from the reference line is marked in the same way (e.g. Ls-EL). An angle is expressed by three points with the top of the angle represented by the middle point (e.g. N-S-tGn) or as a fraction of the signs designating the reference lines which form the angle (e.g. NSL/ML).

In double contours resulting from differences between right and left images, points were marked at the midpoint between both contours.

A positive value of the angle ANB means, that the point A is in an anterior position toward B. A negative value of the angle means the posterior position of the point A. According to the ANB angle the patients subdivided into three skeletal classes (Table 4). The angle N-A-Po expresses the amount of facial convexity, but this value in Table 2 marks the difference between the angle of 180° and the angle N-A-Po. A negative value of the convexity indicates, that the point A is situated in

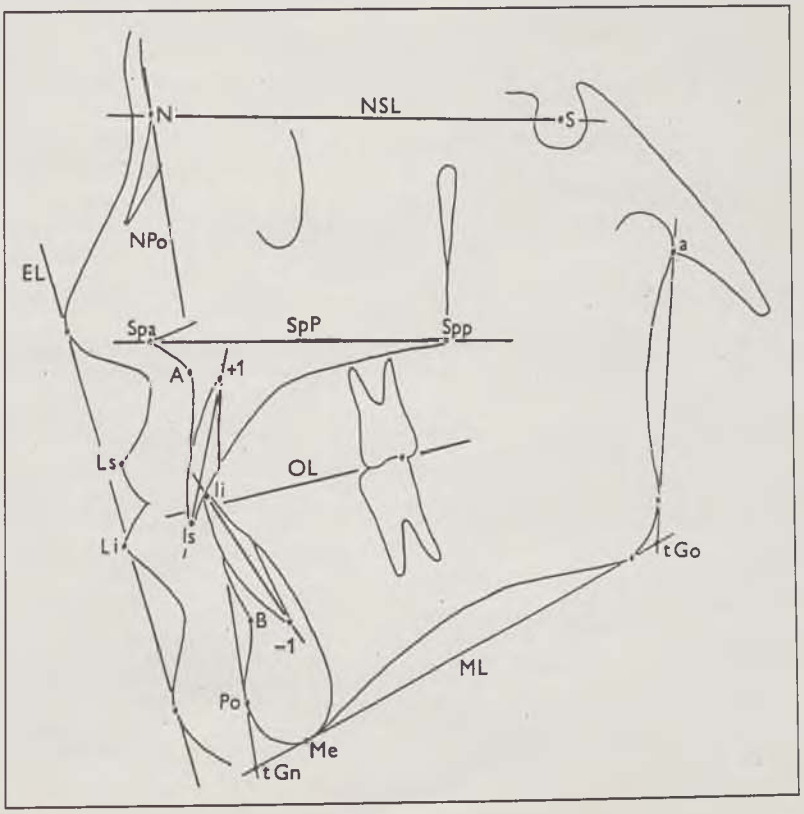

Fig. 1: Cephalometric points and reference lines used in the present study. Points: N - nasion, S - sella, a - articulare, tGo - gonion obtained as intersection of tangents to the mandibular body and ramus, Me - menton, tGn - gnation obtained as intersection of lines ML and NPo, Po - pogonion, Spa - spina nasalis anterior, Spp - spina nasalis posterior, A - subspinale, Is - incision superius, Ii - incision inferius, B - supramentale, Ls - labrale superius, Li - labrale inferius. Reference lines: NSL - line through N and S, ML - tangent to the mandibular body through Me, SpP - line through Spa and Spp, OL - line through the midpoint between the tips of the upper and lower incisors and the point on the top of the posterior tubercle of the first lower molar (line of occlusion), +1 - axis of the upper central incisors, -1 - axis of the lower central incisors, NPo - line through N and Po (facial line), EL - tangent to the top of the nose and to the soft tissue contour of the chin.

the posterior position toward the line N-Po. The growth rotation of the face is expressed like S-tGo % N-Me (S-tGo in percent of N-Me). If the relationship is smaller than 59%, the face is in a posterior growth rotation (CW), if it exceeds 63%, the face is between 59-63%, the growth is neutral (N) (Table 4). An overjet (OJ) is the antero-posterior distance between the tips of upper (Is) and lower (Ii) incisors, its value is negative, if the point Is lies behind Ii. An overbite (OB) is the vertical distance between the tips of incisors. A negative value of the overbite means an open bite. The distance of the tips of upper and lower incisors from the facial line (NPo) is expressed by a negative value, if the tips of the incisors do not attained the line in the anterior direction. The characteristics Ls-EL and Li-EL show the perpendicular distance of the upper and lower lip from the Ricketts estetic line.

The measurements were analyzed with standard statistical method. For the illustration of linear growth rate, mean increments of dimensional change throughout each period (5-10 y., 10-15 y., 15-20 y.) of age are expressed in terms of percent of the initial value of the given period. The magnitude of increments and of developmental changes was tested with the paired t-test. The average coefficient of reliability of measurements was 99.7%.

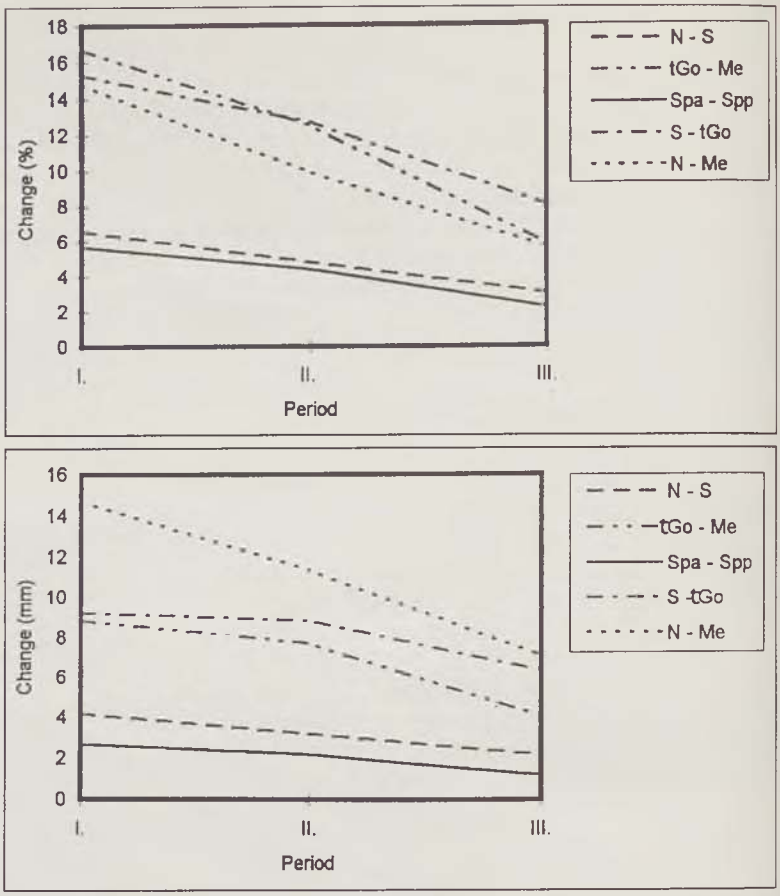

Fig. 2: The curves of growth changes of certain linear characteristics in prepubertal (I.), pubertal (II.) and postpubertal (III.) period in terms of percents (a) and in mm (b).

RESULTS

Amount of growth

Results are presented in Table 1 and in Figure 2a and 2b. The growth of the cranium is approximately the same in the prepubertal (5-10 years) and in the pubertal (10-15 years) period - from 5.7% to 16.7% in different measured characteristics. The maximum growth in the pubertal period is by 5% smaller than in the prepubertal period. It is markedly smaller in the postpubertal period (15-20 years), it ranges between 2-9% of the value recorded at the age of 15 years.

During the prepubertal and pubertal period the highest growth rate show vertical dimensions:

Table 1. Mean values of X-ray cephalometric characteristics of the size at the age of 5 and 20 years (mm) and growth changes in three investigated periods

period variable	5 years I. series	5-10		10-15		15-20		20 years II. series
		mm	%	mm	%	mm	%	
N-S	63.45	4.17***	6.6	3.22***	4.8	2.18***	3.0	74.68
S-a	27.53	4.92***	17.9	4.00***	12.3	1.81***	5.0	38.22
a-tGo	36.93	4.57***	12.4	5.09***	12.3	4.36***	9.4	50.96
tGo-Me	53.08	8.85***	16.7	7.72***	12.5	4.08***	5.8	74.84
tGo-tGn	59.76	9.77***	16.3	7.44***	10.7	4.13***	5.3	82.26
Spa-Spp	46.93	2.69***	5.7	2.17***	4.4	1.18**	2.2	54.31
N-tGo	96.88	11.57***	11.9	9.83***	9.1	6.88***	5.7	128.29
S-tGn	102.19	15.86***	15.5	12.50***	10.6	7.77***	5.9	138.71
S-tGo	60.29	9.23***	15.3	8.85***	12.7	6.35***	8.0	85.57
N-Me	99.55	14.73***	14.8	11.34***	9.9	7.10***	5.6	134.09

Significant increment of the variable at *p < 0.05, **p < 0.01, ***p < 0.001

the posterior length of the cranial base (S-a, 18 and 12%), posterior facial height (S-tGo, 15 and 13%), anterior facial height (N-Me, 15 and 10%) and the length of the mandibular ramus (a-tGo, 12%). A smaller growth increment (6 and 4%) was found in the length of the maxilla (Spa-Spp) contrary to the length of the mandibular body (tGo-Me and tGo-tGn, 29-31%). The depth (N-tGo) and the length (S-tGn) of the face showed larger growth changes, approximately between 9 and 16%. The anterior part of the cranial base (N-S) increased by about 7 and 5% in the prepubertal and pubertal period while in the postpubertal period growth amounted only to 3%. In the postpubertal period showed the very little growth changes the length of the maxilla as well (2.%). In contrast to this, the ramus of the mandible increased further by about 9%. The growth of other vertical dimensions of the face and of the length of the mandibular body amounted to about 5.5% in the postpubertal period of age.

Developmental changes

Results are presented in Table 2 and 3. The angle of the cranial base (N-S-a) decreased only in the postpubertal period. The mandible was posteriorly rotated (N-S-tGn) only in the prepubertal period with a retroinclination of the mandibular ramus (S-a-tGo). The steepness of the mandibular body increased in the prepubertal period insignificantly (NSL/ML) in spite of the increase of the lower part of the gonial angle (N-tGo-Me). The upper part of the gonial angle (a-tGo-N) decreased by the same value during this period. Thus the gonial angle (a-tGo-Me) did not change. There was an anterior rotation of the palatal plane (NSL/SpP).

In the pubertal period the steepness of the mandibular body (NSL/ML, N-tGo-Me) and the posterior growth rotation of the mandible (N-S-tGn) were reduced. This development resulted in an improvement of vertical jaw relations after the age of 10 years. The protrusion of the lower jaw (S-N-Po, SNB) increased during all studied periods, while the anterior growth of the maxilla was reduced (SNA) in the prepubertal period. Sagittal jaw relations (ANB) deteriorated in all investigated periods. Up to the age of 15 years they deteriorated in all patients and after the age of 15 years in about 75% of the patients. While at the

Table 2. Mean values of angular X-ray cephalometric characteristics at the age of 5 and 20 years (degree) and developmental changes in three investigated periods (minus sign showes the decrease of the characteristic during given period)

period variable	5 years I. series	5-10	10-15	15-20	20 years II. series
N-S-a	126.84	-0.25	-0.47	-0.85**	124.97
S-a-tGo	138.62	2.10***	1.37	1.98***	147.35
a-tGo-Me	134.37	-0.97	-2.24***	-2.22***	125.78
a-tGo-N	57.28	-2.97***	-2.28***	-2.13***	47.93
N-tGo-Me	77.19	2.00***	0.09	-0.11	77.79
NSL/ML	39.90	0.88	-1.31***	-1.03**	38.18
SpP/ML	32.14	2.07**	-1.29***	-0.75	31.56
NSL/SpP	8.02	-1.16*	-0.27	0.03	6.82
SNA	77.34	-3.29***	-0.81*	-1.03***	72.06
SNB	72.17	0.69*	1.55***	0.49*	73.40
ANB	5.22	-3.98***	-2.45***	-1.58***	-1.37
N-S-tGn	71.62	1.04**	-0.16	0.00	73.08
S-N-Po	72.14	1.72***	1.90***	0.85***	75.56
N-A-Po	10.03	-9.77***	-5.19***	-3.74***	-6.84
OL/ML	20.71	0.74	1.52***	1.91***	23.26
+1/-1	165.45	-18.33***	-4.15*	-2.75	141.09
-1/ML	80.32	1.98*	-1.10	0.63	83.72
-1/NSL	74.14	15.60***	4.50	3.08**	96.99

Significant increment of the variable at *p < 0.05, **p < 0.01, ***p < 0.001

Table 3. Mean values of linear X-ray cephalometric characteristics at the age of 5 and 20 years (mm) and developmental changes in three investigated periods (minus sign showes the decrease of the characteristic during given period)

period variable	5 years I. series	5-10	10-15	15-20	20 years II. series
Ii-ML	34.31	4.86***	4.43***	2.28***	46.06
Is-NPo	0.66	0.44	-0.81	-1.06**	0.26
Ii-NPo	1.21	-0.14	-0.95*	-0.64**	-0.70
overjet	-0.59	0.61	0.12	-0.42	1.01
overbite	0.53	0.30	-0.31	-0.81**	0.22
Ls-EL	-1.02	-2.60***	-2.47***	-2.42***	-8.32
Li-EL	0.78	-0.83*	-1.02**	-0.85**	-2.56

Significant increment of the variable at *p < 0.05, **p < 0.01, ***p < 0.001

age of 5 years the ANB angle was larger tan 0° in all patients, one half of adults had a negative angle ANB (Table 4). The higher growth of the mandibular body length as compared to the minimum growth of the length of the upper jaw and an increasing protrusion of the mandible (S-N-Po) led to a flattening of the facial profile (N-A-Po). Up to 15 years of the age the profile flattened in all patients, in the postpubertal period still in about 85% of the patients. In the pubertal and postpubertal period the angle between occlusal and mandibular plane (OL/ML) increased significantly.

Table 4. The subdivision of patients into skeletal classes according to the ANB angle at the age of 5 and 20 years and changes of the skeletal class in three investigated periods in percents of the total number of patients (I. -> ANB = 0°-5°, II. -> ANB > 5°, III. -> ANB < 0°)

skeletal class age (years)	I.	II.	III.
5	48.3	51.7	0.0
20	41.2	0.0	58.8
period (years) change of class	5-10	10-15	15-20
I.->III.	27.6	24.1	29.5
II.->I.	44.8	6.9	2.9
II.->III.	3.4	0.0	0.0
without change	24.2	69.0	67.6

The type of growth rotation of the face is expressed by the relation of the posterior to the anterior height of the face (S-tGo%N-Me, Table 5). The growth rotation did not change in three quarters of the patients. If the rotation changed with age, in the predominant part of individuals it changed from neutral growth to anterior growth rotation.

Table 5. The type of growth rotation of the face at the age of 5 and 20 years and changes in growth rotation in three investigated periods in percents of total number of patients (CCW = anterior growth rotation, CW = posterior growth rotation, N = neutral growth)

type of rotation age (years)	CCW	CW	N
5	20.7	31.0	48.3
20	55.9	11.8	32.3
period (years) change of rotation	5-10	10-15	15-20
N->CCW	20.7	17.2	11.8
CW->N	0.0	6.9	2.9
CCW->N	3.4	0.0	0.0
without change	75.9	75.9	85.3

In the dental region occurred changes in the interincisal angle (+1/-1). The angle decreased in the prepubertal period, because of the improvement in the retroinclination of upper incisors (+1/NSL). The inclination of lower incisors (-1/ML) did not change. At the age of 5 years developed on the average an anterior crossbite. Up to 15 years of age the overjet slightly improved, while on the contrary it deteriorated during the postpubertal period. However all changes were insignificant.

The configuration of the soft profile reflected skeletal changes. In Jarabak's analysis are only two characteristics for an assessment of the soft tissue distance of the upper and lower lip from the estetic line (Ls-EL, Li-EL). The retrusion of the maxilla was associated with an increasing distance of the upper lip from the estetic line. The displacement of the lower lip was slighter than that of the upper lip.

DISCUSSION

The growth of facial structures attained during the prepubertal period was on the average 13.3% of the initial value recorded at the age of 5 years. During the pubertal period growth was approximately 9.9% of the value at the age of 10 years and in the postpubertal period increments were 5.6%. The greater growth during the prepubertal than pubertal period is probably due to the eruption of permanent incisors and first molars. It also results from a small pubertal spurt which is typical for facial parameters (Baughan et al.).

The upper jaw length increased very slightly in all periods. This was due to the primary surgical repair of the palate (Šmahel and Müllerová, 1986).

The growth of the anterior part of the cranial base was small as well. Roche et al. (1977) state, that the growth of the anterior cranial base is finished early during childhood (at 6 years). In contrast, the growth of the posterior part of the cranial base continues up to 18 years of age. This was confirmed by Šmahel et al. (1993) as well. It is caused by active growth of the posterior part of the base from the sphenooccipital synchondrosis, while the anterior part grows exclusively by aposition in the region of the radix nasi (Šmahel and Müllerová, 1994). The angle of the cranial base changes only slightly in the postpubertal period.

Mandibular deviations are independent of the degree of maxillary retrusion (Šmahel and Brejcha, 1983). The body and ramus of the lower jaw are shorter at the age of 5 years than in normal populations, but the postoperative growth of the mandible is the same (Šmahel et al., 1993). The increments of the length of the mandibular body and ramus were the same in the prepubertal and pubertal periods; in the postpubertal period the growth of the lower jaw decreased markedly. This does not agree with the results of Šmahel and Müllerová (1996), who found nearly the same growth of the mandible in boys in the pubertal and postpubertal periods. Retroinclination of the mandibular ramus can be caused by a therapeutic effort to restore a positive overjet (Šmahel et al.,

1993). In our patients, the retroinclination of the ramus was marked in the prepubertal period and the overjet was improved only in this period. The largest growth of the body of the lower jaw in the anterior direction occurred in the pubertal period. The difference between the angle SNB and S-N-Po could be caused by deepening of the supramental concavity.

The shortening of the ramus of the mandible results in flattening of the gonial angle (a-tGo-Me), increase of the body steepness (NSL/ML) and an elongation of the anterior height of the mandible (Šmahel and Škvařilová, 1988). These changes could compensate the unfavourable sagittal jaw relations. The gonial angle becomes smaller with age, but less than in normal populations (Paulin and Thilander, 1991). The decrease occurred only in the pubertal and postpubertal periods.

Impairment of vertical jaw relations (SpP/ML), is caused also by anterior rotation of the palatal plane in the prepubertal period. Šmahel et al. (1993) showed that it is caused by more intensive growth of the posterior height of the upper face (S-Spp) as compared to the anterior height (N-Spa). It could be „catch up" growth (Hellquist et al., 1983).

Impairment of sagittal jaw relations is caused by the retrusion and insufficient anterior growth of the upper jaw. The larger tension of the restored lip causes retroinclination of the upper incisors (Hayashi et al., 1976). Inclination was improved in the prepubertal period by orthodontic therapy, with restoration of a positive overjet. The overjet impaired again in the postpubertal period. Paulin and Thilander (1991) consider the improvement of occlusion between 5 and 15 years of age as a consequence of orthodontic treatment. The impairment of the occlusion in the opinion of Šmahel and Müllerová (1995) results from the exhaustion of compensatory mechanisms of the jaws caused by previous orthodontic treatment. The impairment of sagittal jaw relations causes a flattening of the face. The skeletal profile become concave in the pubertal period. This was also noted by Semb (1991).

Growth rotation of the face is expressed in Jarabak's analysis as a relationship of the posterior and anterior height of the face (S-tGo%N-Me). This relationship showed in our patients a reduction of the anterior growth rotation. However this growth pattern did not change in 75% of patients. Šmahel and Müllerová (1994) do not recommend the use of the relationship of the heights of the face for assessment of growth rotation. They recommend assessment angles, which describe the steepness of the mandibular body.

The assessment of the soft tissue profile contains, in Jarabak's analysis, only distances of the lips from the estetic line. However, it can be influenced by flattening of the apex of the nose and by chin prominence. Therefore assessment of the soft profile according to Jarabak's analysis is insufficient in facial clefts.

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ANTHROPOMETRICAL MEASUREMENTS OF THE FACE IN INFANTS WITH BILATERAL CLEFTS

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SUMMARY

The anthropometric measurements of face were taken in 21 infants of 6 - 9 months (15 boys, 6 girls) with bilateral cleft lip, alveolus and palate, prior to surgery. The control group consisted of 30 normal infants, without facial defects. In each child 9 measurements were performed. The comparative analysis revealed an underdevelopment of maxilla and mandible and an increase in nasal width in children with bilateral cleft lip and palate.

ZUSAMMENFASSUNG

Die anthropometrischen Gesichtscharakteristiken bei Säuglingen mit beiderseitiger Lippen- und Gaumenspalten

B. Antoszewski, J. Kruk-Jeromin

Das Gesicht von 21 Säuglingen im Alter von 6 - 9 Monaten (15 Jungen und 9 Mädchen) mit beiderseitiger Lippen-, Kiefer- und Gaumenspalten wurde vor der Lippenoperation anthropometrisch untersucht. Die Kontrollgruppe bildeten 30 gesunde Personen. Bei Kindern mit beiderseitiger Lippen- und Gaumenspalten wurde eine Inzuffizienzentwicklung des Ober- und Unterkiefers und die Vergrößerung der Nasenbreite nachgewiesen.

Key words: cleft lip and palate, anthropometry

Cleft lip, alveolus and palate is a congenital malformation, consisting in a lack of anatomical continuity and the underdevelopment of these structures. The causes of the defect have not been conclusively explained. One of the most popular hypotheses is the multifactorial genetic - environmental pattern. The etiopathogenetic factors result in development disturbances of the mesoderm and in the lack of ectodermal continuity, which lead to the birth of a child with a cleft within the upper lip, alveolus and palate. The clinical pattern varies according to the magnitude and type of deformation. Thus, the problems of classification of clefts arise. In the Department of Plastic Surgery of the Medical University of Łódź we have adopted the classification of clefts, according to Bardach and Perczyńska-Partyka (2), based on anatomical disorders. Thus, the general classification of clefts comprises 5 groups: I - lip, II - lip and alveolus, III - palate, IV - lip, alveolus and palate, V - combined clefts.

The bilateral cleft lip, alveolus and palate is the most serious form of clefts and occurs in 11.3% of all clefts, as was revealed by analyzing the births in łódź in 1982 - 1991 (1). The lack of continuity within the upper lip and a connection between the oral and nasal cavities result in numerous functional disorders, mainly in difficulties in sucking and swallowing by the afected infant, and later on in impaired speech (2, 10).

The polymorphism of the defect, extent of deformations within several systems create the necessity of a team approach towards children with clefts, with cooperation of different specialists (2, 3, 5, 7-10). On normal conditions, facial development depends on many factors. The bony growth centres, the activity of the muscular system and physiological factors play an important role (6). In clefts, those conditions may change to a greater or lesser extent which influences the displacement of maxillary segments and soft tissues (4). There is a possibility to apply the anthropological study on the proper growth of human body in practise.

MATERIAL AND METHODS

The aim of this study is to define whether the group of children with bilateral complete clefts

Table 1. The cephalometric characteristics in infants with bilateral cleft lip and palate compared to controls (mv = mean value)

Variable	Clefts		Controls		Statistics	
	mv	SD	mv	SD	t-test	p
g - op	148,14	4,175	146,87	3,919	1,109	0,280
eu - eu	123,10	3,714	124,37	4,214	-1,111	0,276
ms - ms	98,05	4,566	100,27	2,778	-2,158	0,039*
ft - ft	87,86	3,214	90,10	2,759	-2,666	0,0123*
zy - zy	101,52	4,332	104,27	4,563	-2,162	0,0392*
go - go	76,24	2,827	79,00	3,414	-3,043	0,0050*
n - gn	72,81	5,221	73,97	3,102	-0,994	0,33
n - sto	51,17	5,037	49,33	2,412	1,741	0,092
n - sn	34,14	2,330	32,33	2,023	2,954	0,0062*
al - al	33,29	3,227	24,77	1,755	12,151	0,00005*

*statistically significant difference at $p < 0.05$

differs from normal and how. 21 infants (15 boys and 6 girls) of 6 - 9 months (mean age 6 months and 17 days), with bilateral cleft lip, alveolus and palate and birth weight over 2800 g, have been subjects of anthropometric measurements, prior to surgery. All children were subjected to multispecialist care in the Centre for Treatment of Congenital Defects, at the Department of Plastic Surgery, since 3 - 6 weeks of life. During the presurgical period all children wore a subnasal band and had their premaxillas massaged. The control group comprised 30 normal infants, 21 boys and 9 girls of 6 - 9 months (mean 6 months and 21 days) from creshes of Łódź, who had no facial defects, were born in a natural way, on time and whose birth weight was over 2800 g. Each child's head was measured with spreading and sliding callipers with a precision of 1 mm. The anthropometric measurements included: 1) length of head - e.i. distance between the glabella - opisthokranion (g - op), 2) width of head - distance between the lateral points of head euryon - euryon (eu - eu), 3) the shortest width of forehead - distance between both points frontotemporale (ft - ft), 4) morphological height of the face - distance between points nasion - gnathion (n - gn), 5) the largest width of the midface - distance between points zygion - zygion (zy - zy) 6) width of the lower face - distance between points gonion - gonion (go - go), 7) distance between the mastoid processes (ms - ms), 8) width of nose at the level of alae (al - al), 9) height of nose (n - sn). The results were statistically analysed with the t-test. No significant differences between male and female infants were found. Thus both sexes were pooled.

RESULTS

The results of measurements were compared with those in controls (tab. 1). The research revealed: an underdevelopment of the maxilla, resulting in changes of the facial width at the level of zy - zy points, mandibular retardation presenting as a reduction of the go - go dimension, decrease in the distance between the mastoid processes (ms - ms) and between both points frontotemporale (ft - ft), and an increase in the nasal width and height.

The changes due to the underdevelopment of the midface, towards the smaller dimensions of upper and lower face, are not a rule, since the nature of development of these regions is only indirectly related to the development stage of jaws. The abnormally wide nose with its increased height indicates possible disproportions between the width and height of the nose and between the nasal and facial widths, as it was reported by Farkas (4).

CONCLUSIONS

The earlier anthropometric research, revealing some discrepancies in the form of the head in children with cleft lip and palate is insufficient for the clinician, who deals with cleft surgery. The variability of forms of clefts requires individualized method of measurements, taking into consideration the disorders in facial symmetry, and incorporation of additional measurements of both nasal sides and allowing for anthropometry of left and right side of face.

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DIFFERENT EMBRYOTOXIC EFFECT OF VITAMIN A AND B-CAROTENE DETECTED IN THE CHICK EMBRYO

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SUMMARY

Teratogenicity of vitamin A was firstly detected in experimental animals in 1953. Nearly 30 years later, teratogenicity of vitamin A analogue - isotretinoin was reported in humans. Isotretinoin induces serious birth defects of craniofacial and central nervous system, cardiovascular system and thymic malformations - in about 25% of babies exposed during the first trimestr of their prenatal development. The biological interconversion of isotretinoin to vitamin A is known. That is why later epidemiological studies focused on high vitamin A intake in pregnant woman: Women who use daily vitamin A supplements during early pregnancy have approximately a two-fold increased risk of giving birth to a malformed baby. On the basis of these data, replacement of vitamin A has been recommended with its natural precursor B-carotene which is supposed to be more safe for pregnant woman due to its limited absorption from intestine.

Aim of the present paper was to test a possible direct embryotoxic effect (i.e. lethality + teratogenicity) of B-carotene in chick embryos and to compare these results with known embryotoxicity of vitamin A in the same experimental model. Single subgerminal or intaamniotic injection of vitamin A or B-carotene within day 2-5 of incubation was used for estimation of the beginning of the embryotoxicity range determining the minimal embryotoxic doses. Vitamin A started to affect development between doses 0.3-0.3 mmmg per embryo. Malformations of head, extremities and heart were detected similarly like in laboratory mammals and in man. B-carotene exhibited such an effect neither after injection of the highest tested doses - 100 mmmg per embryo. The results documented the strong difference in embryotoxicity between vitamin A and B-carotene. After theoretical extrapolation of the results achieved in the chick embryo, the minimal embryotoxic doses of vitamin A in mammals were estimated to be between 0.1-1 mg/kg of maternal weight and those of B-carotene to be more than 1000 mg/kg of maternal weight. Human epidemiological studies have proved teratogenicity of vitamin A after daily doses 25 000 IU - 8.3 mg (0.13 mg/kg) - and reduction of its maximum intake has been recommended to 10 000 IU per day (0.05 mg/kg). The results about teratogenicity of vitamin A achieved in the chick embryo are in agreement with such a recommendation. Intake of vitamin A in the food is sufficient for pregnant woman in common Czech population. Therefore, an artificial supplementation of vitamin A brings risk of overdosage. If supplementation by vitamin A is unavoidable during pregnancy, B-carotene should be prefered.

ZUSAMMENFASSUNG

Der Unterschied in der Embryotoxizität der Vitamine A und B-Karotten, der im Huhnfetus mit der CHEST Methode festgestellt wurde

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Die teratogenne Auswirkung des Vitamins A wurde bei den Laboratorsäugetieren schon im Jahre 1953 entdeckt. Fast 30 Jahre später wurde die Teratogenizität der Analogen des Vitamins A-Isotretinoin bei dem Menschen festgestellt. Bei 25% der Neugeborenen, die während des ersten Trimesters der Schwangerschaft exponiert wurden, rufte Isotretinoin schwere angeborene Fehler des kraniofazialen Gebietes, die kardiovaskularen Fehler und die Fehler des Milchfleisches hervor. Die biologische Konversion des Isotretinoins ans Vitamin A ist allgemein bekannt. Deshalb richteten sich die epidämiologischen Studie auf die Schwangerschaften der Mütter, die das Vitamin A in hohen Dosen eingenommen haben. Denjenigen, die täglich das Vitamin A während der frühen Phasen der Schwangerschaft eingenommen haben, drohte zweimal höheres Risiko, daß sie ein Kind mit angeborenem Fehler bekommen. Deshalb wurde empfohlen das Vitamin A mit seinem natürlichen Prekusor B-Karotten zu ersetzen, bei dem vorausgesetzt wird, daß es für schwangere Frauen viel sicherer dank der beschränkten Aufsaugung aus dem Darm ist. Das Ziel unserer Studie was die mögliche direkte Auswirkung des B-Karottens auf den Huhnfetus zu testen und vergleichen die Ergebnisse mit der bekannten Embryotoxizität des Vitamins A am identischen experimentalen Modell. Für die Schätzung des Anfangs der Embryotoxizität (d.h. nach der Bestimmung der minimalen embryotoxischen Dosen des Vitamins A und B-Karottens) wurde die subgerminale oder intraamniale Spritze den Huhnfetusen im Alter vom 2.-5. des embryonalen Tages apliziert. Das Vitamin A begann die Entwicklung des Embryos im Abschnitt der Dosen 0.3-0.03 mmmg zu stören. Es wurden die Malformationen des Kopfes, der Extremitäten und des Herzens festgestellt - ähnlich wie es bei den Laboratorsäugetieren und dem Menschen war. B-Karotten beschädigte die Fetusen auch in den höchsten getesten Dosen - 100 mmmg nicht. Die Ergebnisse dokumentieren den großen Unterschied zwischen der direkten Embryotoxizität des Vitamins A und B-Karottens. Nach der theoretischen embryotoxischen Dosen des Vitamins A für Säugetiere zwischen 0.1-1 mg/kg Gewicht der Mutter und B-Karottens höher als 1000 mg/kg Gewicht der Mutter. Die epidämiologischen Studien erwiesen Teratogenität des Vitamins A beim Menschen nach täglichen therapeutischen Dosen 25 000 IU - 8.3 mg (0.13 mg/kg) und es wurde empfohlen das Vitamin A nicht in den täglichen Dosen über 10 000 IU (0.05 mg/kg) einzunehmen.

Unsere Ergebnisse über die am Huhn gewonnen Teratogenität des Vitamins A stimmen dieser Empfehlung zu. Der Inhalt des Vitamins A in den Lebensmitteln ist in der normalen tschechischen Population für schwangere Frauen genügend und deshalb die Einnahme des Vitamins A in der Arzneiform trägt in sich das Risiko der Überdosierung. Unsere Ergebnisse bestätigen die Ansicht, daß in den Fällen, wann das Vitamin A in der Schwangerschaft notwendig ist, ist besser es mit B-Karotten zu ersetzen.

Key words: B-carotene, Beta carotene, CHEST, embryotoxicity, retinoic acid

In 1953, Cohlan published preliminary results of the first study revealing teratogenic effect of excessive doses of vitamin A in rat (Cohlan, 1953). The full report was published one year later (Cohlan, 1954). Since that time, the teratogenicity of retinoids have been confirmed in all experimental mammals and in the chick embryo: The cleft palate, limb reductions, heart and eyes defects represent the most frequent malformations induced by vitamin A (Kalter, Warkany, 1961; Kochhar, Johnson, 1965; Shenefeld, 1972; Jelínek, Kistler, 1981). In 1983 the first malformed babies resulting from exposure to isotretinoin (13-cRA), a synthetic derivate of vitamin A were reported (Rosa, 1983). Isotretinoin was approved for treatment of severe cystic acne in 1982. The pattern of major malformations involved developmental defects of face and cranium, heart, thymus and brain (Lammer et al., 1985; Lammer, 1987). It has been determined that the relative risk of origin of a malformation is approximately 25% among fetuses that reach 20 weeks of gestation following maternal exposure to therapeutic doses (Lammer et al., 1987). Lammer's reports (Lammer 1985; 1987) on the teratogenic effects of a vitamin A analogue gave rise to hypothesis about possible direct teratogenicity of vitamin A in humans. Approximately a two-fold increased risk of giving birth to an infant affected by a malformation was found in epidemiological study in women that used vitamin A supplements daily during early pregnancy (Werler et al., 1990). One of the last reports about teratogenicity of high vitamin A intake has estimated, that one malformed baby borns from 57 women which consumed more than 10 000 IU of vitamin A per day from supplements (Rothman et al., 1995). B-carotene and other carotenoids are natural plantsynthesized precursors of vitamin A, that are partially converted to effective retinol either during or after their intestinal absorption in mammals (Wang, 1994). It was recommended, therefore, to substitute vitamin A to B-carotene which is supposed to be more safe for pregnant woman due to its limited absorption from the intestine.

The CHEST (Chick Embryotoxicity Screening Test) is a method, which allows to detect direct effect (lethal and teratogenic) of a tested substance on the embryonic development, without an interaction with maternal metabolic systems (Jelínek, 1977; 1982; Jelínek, Peterka, 1981). This method was used in the present study with aim to test effect of exposure to B-carotene in the chick embryo and to compare the results with known data on embryotoxicity of vitamin A, achieved in the same model. After theoretical extrapolation, embryotoxic doses were estimated also for mammals including man.

MATERIAL AND METHOD

Determination of the embryotoxocity dose-range

The Chick Embryotoxicity Screening Test (CHEST), (Jelínek, 1977; Peterka et al., 1992) was used to estimate the beginning of the embryotoxicity dose range of B-carotene and Vitamin A.

Cold fertile eggs of White Leghorns (Dobrenice farm) were placed horizontally in a forced-draft thermostatic oven and incubated at 37.5 °C and 40%-60% relative humidity. Before administration, the eggs were candled and windowed under aseptic conditions using an electric drill. The vitamin A (Fluka) was sonificated and diluted in MEM, B-carotene was diluted in a destilled water. Both substances were injected in five distinct doses 100, 30, 3, 0.3 and 0.03 mmmg either subgerminally on day 2 or intraamniotically on day 3, 4 and 5 of incubation using a calibrated glass micropipette. The injected volumes (10 or 3 mmmL) allowed dosage of the test substance, differing as a rule by one order of magnitude. After administration, the windows were closed with glass slides, sealed with paraffin, and eggs were further incubated without rotation. For estimation of the developmental stage of embryos, HH staging (Hamburger, Hamilton, 1951) was used. Each of 5 doses were given singly to groups of 10 embryos on day 2 (HH 11-14), 3 (HH 17-20), 4 (HH 21-24) and 5 (more than 25 HH). The vitality of embryos was evaluated daily and dead embryos were set aside. On day 9, the surviving fetuses were collected, weighed, and examined under a stereolupe. Besides external examination, dissection of the heart was routinely performed for detection of ventricular septal defect and anomalies of great vessels. Gross dose-response relationship was established by summing up the dead and malformed living specimens for each dose and day of administration, respectively. The beginning of the embryotoxicity range was determined as lying between doses where the

dose-response curve crossed the non-specific effect level. The nonspecific level constitutes the maximal background frequency of malformed and dead control embryos that occurs spontaneously and/or is induced by experimental intervention itself. The upper limit of the non-specific effect has been repeatedly calculated as 0.3 (30%). This means that all values situated above this limit are statistically significant.

Analysis of teratogenic and lethal component of embryotoxicity effect

Vitamin A was injected in doses that exhibited the minimum lethal effect but produced the maximum of living malformed embryos. We focused to a proportion of dead and malformed living embryos as well as to a detailed analysis of malformation spectra in the latter group after. Single doses (10, 6, 3, 2 and 1.5 mmmg) of vitamin A were injected in the same way as described above with aim to determine malformation spectra related to different critical periods during day 2-5. The living fetuses were harvested also on day 9 and malformations were evaluated for each of the tested dose and day of administration.

Estimation of the embryotoxicity dose-range in human

The rough order estimation of the beginning of the embryotoxicity range for mammals was calculated according to the mathematical extrapolation (Jelínek, 1977; Peterka et al., 1992).

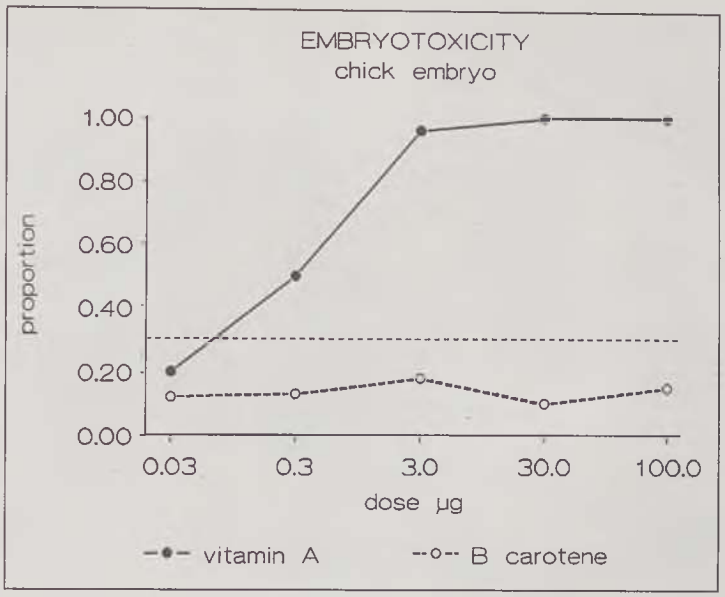


Fig. 1: Mean proportion of malformed+dead embryos (embryotoxic effect) after single injection of five different doses of vitamin A and B-carotene on day 2-5. Dotted line, upper limit of the non-specific effect (30%).

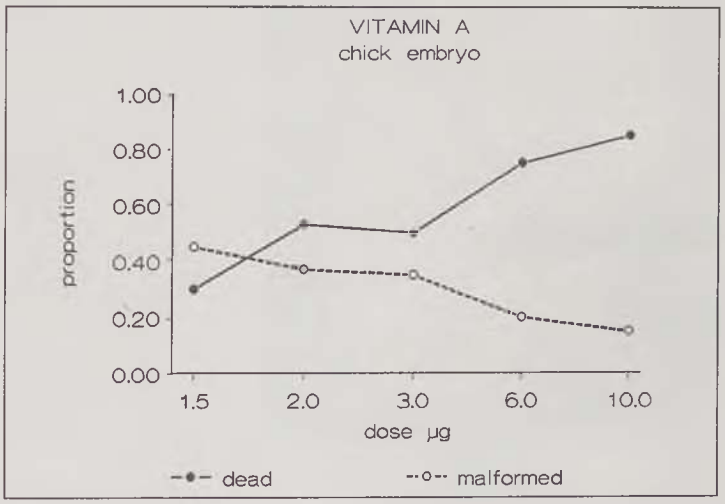


Fig. 2: Mean proportion of malformed or dead embryos after single injection of five different doses of vitamin A on day 2-5. Paradoxically, the number of malformed living embryos decreases with increasing dose as a result of increasing number of dead embryos.

RESULTS

Beginning of the embryotoxicity dose range

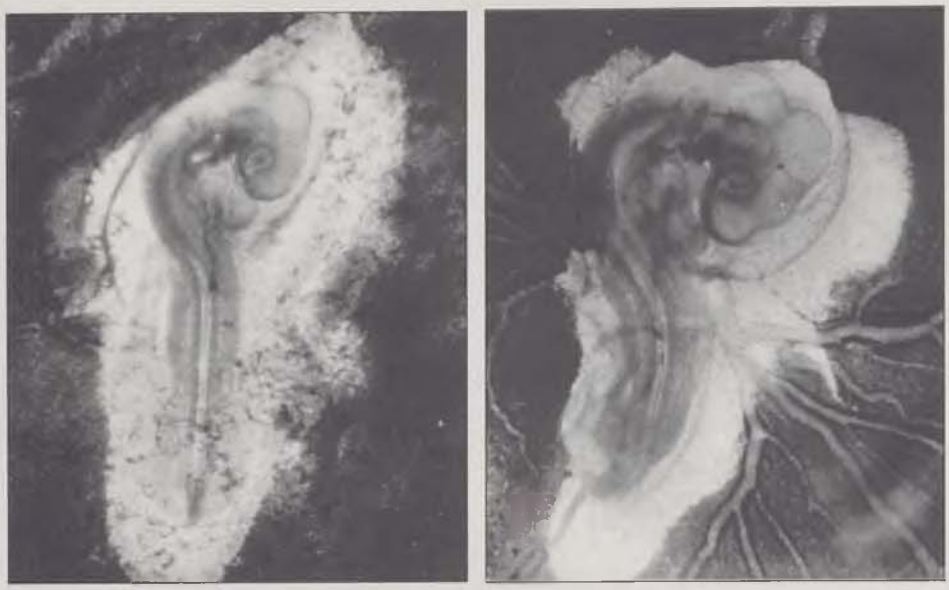
The place of intersection between the dose-response curve and the line of nonspecific effect determined the minimal embryotoxic doses for vitamin A: 0.03-0.3 mmmg per chick embryo (Fig. 1). The highest doses (30 and 100 mmmg per embryo) had a lethal effect in 100% of embryos. B-carotene have no embryotoxic effect even after injection of the highest testing dose 100 mmmg (Fig. 1).

Analysis of embryotoxicity - proportion of dead and malformed embryos

Proportion of dead and malformed living embryos was documented for each day and dose (10, 6, 3, 2 and 1.5 mmmg) of vitamin A administration (Fig. 2). The absolute number of malformed embryos decreased after administration of the high doses due to their extensive mortality. For example, the increase of mortality resulted mostly from anomalous development of vitelline vessels and failure of interconnection between intra- and extraembryonic circulation after administration at early stages (on day 2), (Fig. 3). The reason of embryonic death within days 3-5 was not revealed.

Analysis of embryotoxicity - malformation spectra

The malformation spectrum was determined on the basis of proportion of structural defects related to specific organ systems counted in the living malformed embryos after each dose of vitamin A and day of its administration.



3a) 3b)

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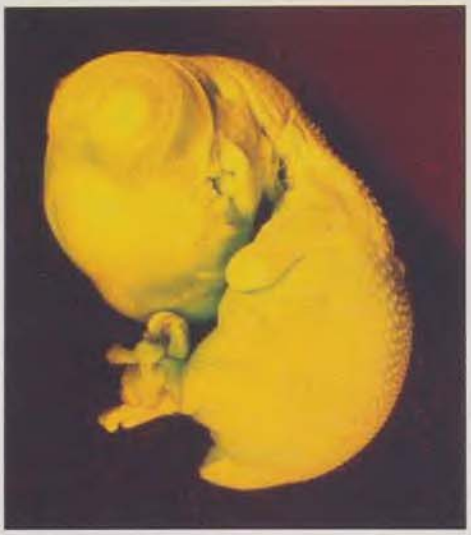
Fig. 3a: Day 3 old control chick embryo documenting normal formation of viteline vessels. 3b: Day 3 old affected chick embryo after injection of vitamin A on day 2. Note absence of the viteline vessels.



←

Fig. 4: Chick embryo day 9 old after injection of 1.5 mmmg of vitamin A on day 3, with severe hypoplasia associated with cleft of the upper beak, and reduction deformity of upper and lower limbs.

At day 2, doses 10 and 6 mmmg of vitamin A had only lethal effect. Maximum malformed embryos were observed after doses, 3, 2 and 1.5 mmmg. Defects of three embryonic components were mainly detected after exposure during this critical period: rumplessness (regression of caudal part of body), gastroschisis (body wall defect) and heart defects (ventricular septal defect and double outlet right ventricle) (Fig. 4).

At day 3 - dose 10 mmmg had only lethal effect. Maximum malformed embryos were found after doses 2 and 1.5 mmmg, which induced affection of heart (isolated ventricular septal defect and an absence of some aortic arch), severe limb reduction, cleft beak, haemocephalus and hypoplasia of eyelids (Fig. 5, 6).

At day 4, all doses produced malformations in surviving embryos with maximum

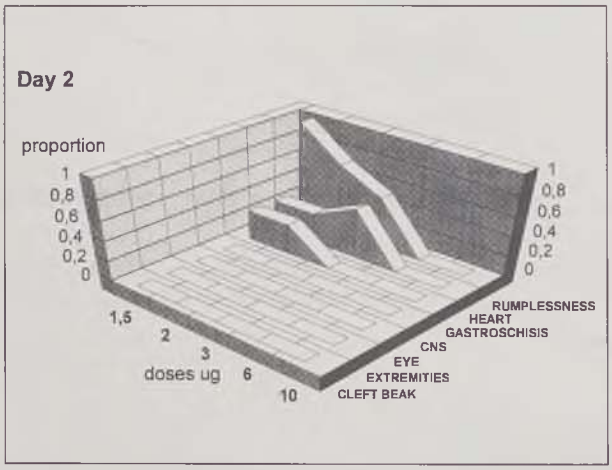


Fig. 5: Proportion of malformed organs in population of day 9 old living affected embryos after single subgerminal injection of 5 doses of vitamin A on day 2.

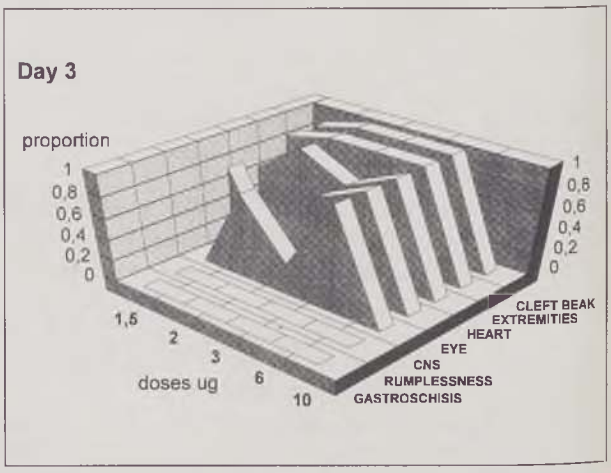


Fig. 6: Proportion of malformed organs in population of day 9 old living affected embryos after single intraamnial injection of 5 doses of vitamin A on day 3.

between doses 3 - 1.5 mmmg. In comparison with day 3, the results were similar except for haemocephalus, which was missing (Fig. 7).

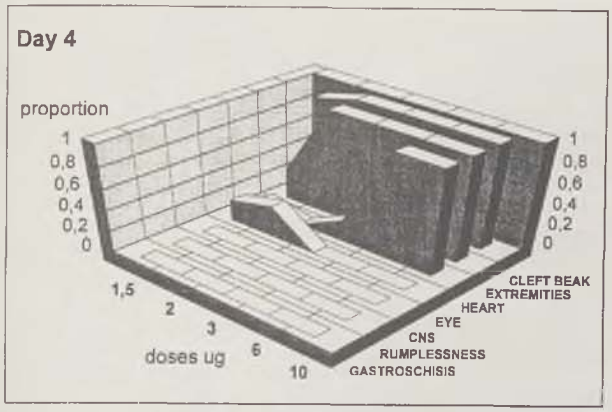


Fig. 7: Proportion of malformed organs in population of day 9 old living affected embryos after single intraamnial injection of 5 doses of vitamin A on day 4.

At day 5, the maximum living malformed embryos were detected after doses 10, 6 and 3 mmmg. They exhibited similar malformation spectra to day 3 and 4 (Fig. 8).

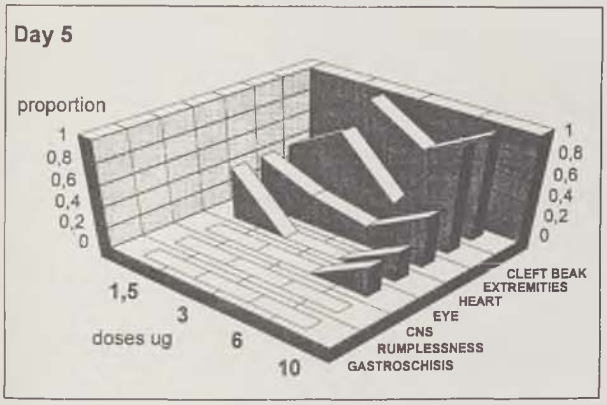


Fig. 8: Proportion of malformed organs in population of day 9 old living affected embryos after single intraamnial injection of 5 doses of vitamin A on day 5.

Estimation of the embryotoxic dose-range for mammals and man

Extrapolation of results on minimal embryotoxic doses of vitamin A and B-carotene in the chick embryo to mammals was performed using mathematical formula. After theoretical extrapolation, the minimal embryotoxic doses (assumed to induce lethal and/or teratogenic effect) of vitamin A were estimated for mammals between 0.1-1 mg/kg, while those ones of B-carotene to more than 1000 mg/kg of maternal body weight.

DISCUSSION

Human epidemiological studies report teratogenicity of vitamin A in daily doses 25 000 IU (8.3 mg). It means approximatively 0.13 mg/kg of maternal body weight. To prevent origin of developmental injury, the upper limit for vitamin A daily supplementation have been recommended to 10 000 IU (0.05 mg/kg) in pregnant women (Underwood 1985; Teratology Society Position Paper, 1987). The data achieved already before in the chick embryo (Jelínek, Kistler, 1981) are in agreement with this recommendation. The minimal embryotoxic doses of vitamin A were estimated between 0.1-1 mg/kg of body weight for mammals. Malformation spectra after administration of vitamin A were similar comparing to experimental mammals and man.

B-carotene exhibited an embryotoxic effect on the developing the chick embryo neither after injection of the highest doses. The results documented strong differences between embryotoxis effect of vitamin A and B-carotene. This results supported idea, that B-carotene is more safe for embryo than vitamin A (Underwood, 1985).

On the other way, it is well known that also deficiency of vitamin A can induce birth defects in animals. Carefully controlled animal studies using vitamin A deficient diets in pregnant females have found prenatal loss and severe congenital malformations in offsprings (Giroud, 1954). During postnatal life, deficiency of vitamin A caused xerophthalmia, which can lead to a permanent blindness in man. A question arises whether a vitamin A deficiency can ever arise in healthy people with normal food intake? Vitamin A is stored primarily in the liver, and more than 90% of total body stores are found in this organ (Bendich, Langseth, 1989). This reserve of vitamin A in human liver is high enough to compensate its deficiency in food for many months. Vitamin A supplementation does not seem to be necessary for healthy pregnant woman ingesting a balanced diet. Most women do not need to take vitamin A supplements either before or during pregnancy, and those who do that should be under medical supervision (Nelson, 1990).

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BACTERIOSTATIC AND BIOLOGICAL STIMULATION EFFECT OF MEPITEL ON EXPERIMENTAL BURNS ON THE SKIN OF RATS

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SUMMARY

This study was conducted on 200 white Wistar rats weighing about 200 g each. The animals were divided into two equal groups - an experimental one, with Mepitel (SCA Mölnlycke) dressings, and a control group with cotton gauze dressings. Microbiological and histological examinations and measurements of the wounds made on the 3rd, 7th, 14th, 21st and 28th days after the 3rd-degree heat burn was inflicted using the standard method.

The observations included burns with the spontaneous elimination of necroses and healing; wounds after operative total necrectomy of the burnt skin and spontaneous healing; and burns followed by total surgical necrectomy and grafting with allotransplants.

The quantitative results reveal statistically reliable bacteriostatic activity above and under the Mepitel dressing. The histological examination reveals considerable biological activity in the tissues under the Mepitel. This manifests itself as an acceleration in the healing process in the wounds caused by burns and after necrectomy of the burnt skin. Mepitel on the allotransplant on the wound, which was left following the necrectomy of the burnt skin provokes the rapid and early rejection of the allograft. Mepitel's biological activity has also been confirmed by the statistically - reliable data relating to the dynamic changes in the length and breadth of the wounds.

The authors came to the conclusion that, when applied immediately to a burn or a wound left following the necrectomy of skin burns, Mepitel suppresses the development of the microbiological flora and stimulates the normal healing process. Mepitel is not suitable for dressing allotransplants because of the rapid acceleration of their rejection.

ZUSAMMENFASSUNG

Der bakteriostatische und biologische stimulierende Effekt des Verbands mit Mephitel an die experimentale Verbrennung der Rattenhaut

K. Troshev, Z. Kolev, A. Zlateva, S. Shishkov, N. Pashaliev, E. Raycheva-Mutafova

Diese Studie wurde an 200 weißen Ratten „Wistar" durchgeführt, von denen jede gegen 200 Gramm wog. Die Tiere wurden in 2 Gruppen eingeteilt; in der ersten Gruppe wurde die Wunde mit Verbänden mit Mephitel behandelt, in der Kontrollgruppe nur mit baumwollen Verbänden. Die mikrobiologische und histologische Untersuchung und die Messung der Wunde wurde mit der standarten Methode am 3, 4, 14, 21 und 28 Tag nach der verursachten Verbrennung des 3. Grades durchgeführt. Die Beobachtung umfasst die Verbrennung mit standarter Ausscheidung von Nekrosen und die Heilung der Wunde nach der operativen totalen Nekrektomie der verbrennten Haut. Weiter auch die spontane Heilung und die Verbrennungen mit der totalen operativen Nekrektomie mit folgendem Hautlappen mit Allotransplantaten.

Die kvantitativen Ergebnisse erweisen statistisch zuverlässige bakteriostatistiche Aktivität über und unter den Verbänden mit Mephitel. Das histologische Bild illustriert die erhebliche Aktivität der Gewebe unter Mephitel. Es zeigt sich aufgrund der Beschleunigung des Heilprozeßes in den Wunden nach der Verbrennung nach Nekrektomie der verbrennten Haut. Mephitel am Allotransplantat der verbrennten Haut provoziert die frühzeitige und schnelle Elimination des Lappens. Die biologische Aktivität von Mephitel wird auch durch statistisch zuverlässige Daten in der Länge und Breite der Wunden bestätigt.

Die Autoren kommen zum Schluß, daß Mephitel, das unmittelbar an die Verbrennung oder an die Wunde nach Nekrektomie der verbrennten Haut apliziert wird, verhindert der Entwicklung der mikrobialen Flora und stimuliert den Heilprozeß. Mephitel ist nicht geeignet für die Verbände der Allotransplantaten, denn es stark beschleunigt ihre Ablehnung.

The healing of burns, independent of the treatment method, depends to a large degree on the properties of the dressing (6, 18). The local application of medication, temporary biological covers and dressings is designed to limit or even eliminate the local infection and prepare the

wound to accept an autograft or stimulate spontaneous healing (3, 7, 13). The healing process begins at the edge of the wound (15). Immediately after the trauma, this zone can enlarge and deepen, or limit itself and diminish. This depends on the treatment and dressing of the wound in the patient's complete treatment programme. Our experience of the clinical application of Mepitel has demonstrated some new properties in this dressing (17). These qualities were therefore checked again in a special experimental study.

PURPOSE OF THE STUDY

The objective was to follow up the effect of Mepitel on the bacterial flora in the burn, as well as the length and quality of the healing process. The criteria for evaluating the qualities of the dressing in a clinical study (5) are different from those in an experimental study. The experiment creates an opportunity for specific observations and at the same time differs from the conditions prevalent in the clinical treatment of the wounds. In this sense, we did our best to take advantage of the experiment by creating models analogous to the clinical treatment methods.

MATERIALS AND METHODS

The entire investigation was conducted on 200 white rats of the Wistar breed, weighing 200 g each. For each set of specimens and observations, 5 rats were prepared. They were not used for any other specimens or observations. The animals were divided into two groups of equal numbers: 1st group, experimental, with Mepitel on the wounds, 2nd group, with cotton gauze dressings on the wounds.

The research work was performed in three experimental settings - 3rd-degree skin burns; 3rd-degree skin burns with one-stage total blood necrectomy immediately after the trauma; 3rd-degree skin burns with one-stage total blood necrectomy immediately after the trauma and covering the wound with a fresh, full-thickness skin allograft.

The burns were inflicted on all the animals under ether inhalation anaesthesia. The samples for investigation were taken under the same anaesthesia, which then intensified until death ensued.

The animals were fixed on wooden boards and the skin on their backs was mechanically depilated by shearing. The burn was inflicted in the standard manner using equipment modified by Kochetygov (8) at the centre of the animal's back. The heat is applied using a beam, without any contact with the heated capsules in the camera, at a distance of 2 cm from the skin. The degree of the burn is calibrated in advance through the duration of the heat under the control of a subdermally-positioned thermistor electronic thermometer. The dimensions of the camera and of the ensuing burns are 3 x 5 cm or 15 sq. cm. On each occasion, the method ensures a standard wound, which is well tolerated by the animals and which does not require an infusion or other form of treatment (11).

In the second setting, a necrectomy was performed using a scalpel and scissors immediately after the burn, at the macroscopically visible line on the burnt skin.

In the third setting, the wound was caused by necrectomy and was then covered with a full-thickness allotransplant with the same dimensions, taken from the back of a healthy rat and stitched to the edges of the wound using continuous sutures with Polycon antimicrobial thread (Bulgaria).

All the manipulations in the wounds after the trauma were performed with sterile instruments. In the first group, Mepitel 5x7.5 cm was applied to the wounds, followed by 9 layers of cotton gauze. In the second group, only 9 layers of cotton gauze with the same dimensions were applied. The dressings were fixed with separate Polycon stitches to the healthy skin.

Before and after trauma and after recovery from the anaesthesia, the animals were kept in individual plastic cages in the same desinfection, accommodation, temperature, light and food conditions.

On the 3rd, 7th, 14th, 21st and 28th days after the burns were inflicted, an evaluation of the general conditions of the animals was made and material for microbiological investigation was taken in the 1st group above and under the Mepitel and from the wound in the 2nd group. Measurements were made of the length and breadth of the wounds using an elastic tapemeasure. The tissue specimens for histological examination were taken in such a way that they included part of the wound, its edge and part of the surrounding skin up to 1 cm from the edge (16).

The microbiological investigation studied three parameters: the prevailing microbial agent, the number of microbial colonies and an area of 1 sq.cm - the microbial number (14) - and the macroscopic appearance of agar plates with photo registration. The microscopic investigation was performed using a routine method and technique.

The histological slides were also prepared using a routine method and technique with a thickness of 5 microns. Haematoxylin-eosin stains were used after van Giesen for collagen connective tissue and trichromic stains with azan after Haidenhein for the differentiation of connective tissue. The specimens were analysed using a light microscope with a magnification of x 8 and were registered on coloured slides.

The quantitative and numerical data were processed statistically using the variation analysis method (9).

RESULTS

In both groups of animals, three kinds of microbe were isolated: staphylococcus epidermidis, Escherichia coli and staphylococcus aureus were permanent in all three experimental settings, although they were not equal in every situation. Staphylococcus aureus was only found in the wound following necrectomy during the period comprising days 3-14 in both groups of animals.

The microbial number (Figs 1, 2, 3) in the first group of animals with Mepitel is lower (under and on the Mepitel) compared with the second group in the wounds under gauze dressings.

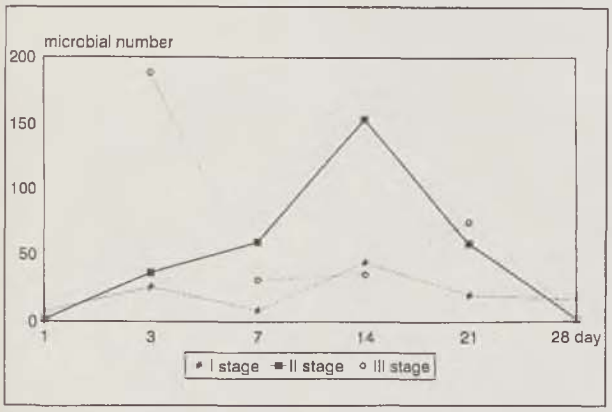

Fig. 1: Dynamics of microbial numbers and the stages of the study depending on the day of observation (wound).

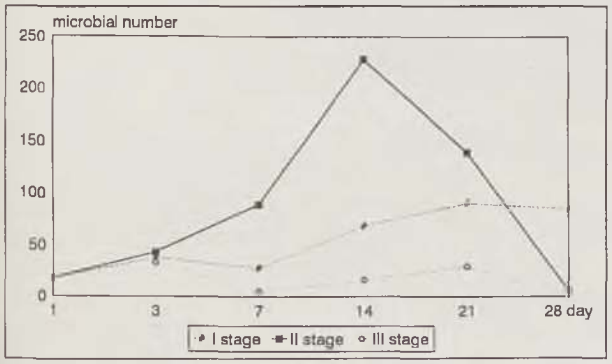

Fig. 2: Dynamics of microbial numbers and the stages of the study depending on the day of observation (bandage).

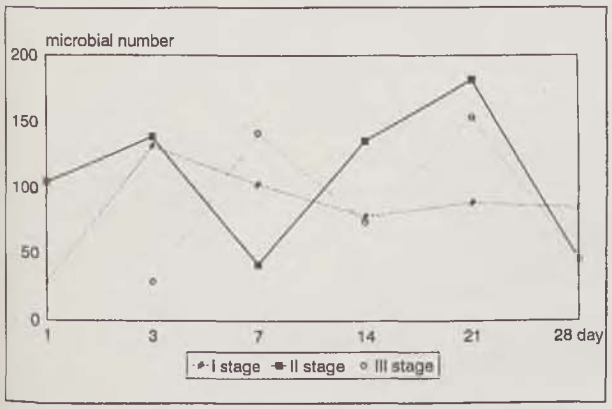

Fig. 3: Dynamics of microbial numbers and the stages of the study depending on the day of observation (control).

In the 1st group, the difference in the microbial number above and under the Mepitel is visible, depending on the specific conditions in the three experimental settings. In the wounds caused by burns above the Mepitel, it is higher than the microbial number under the Mepitel. The relationship on and under the Mepitel in the wounds caused by necrectomy is equal, although the absolute values in the wounds caused by burns are lower. When it comes to the use of Mepitel on allotransplants, this difference is absent and values are equal.

The dynamics in the microbial numbers in the different conditions and in the statistical evaluation maintain their regularity in the experimental setting, in spite of the fluctuation in the dispersion of the absolute numbers.

The macroscopic pictures of microbial growth clearly demonstrate the difference in the growth of colonies above the Mepitel, under it and in the control group.

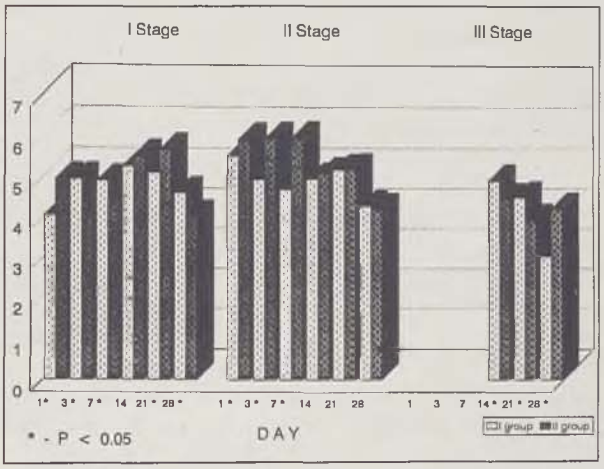

Fig. 4: Changes in the length of the wound by groups and stages of the study.

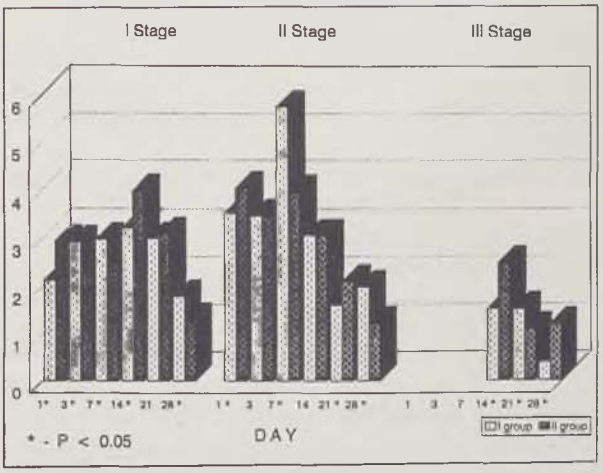

Fig. 5: Changes in the breadth of the wound by groups and stages of the study.

Remarks:
Stage I - the wound after the burn
Stage II - the wound after the burn and blood necrectomy
Stage III - the wound after the burn, necrectomy and fresh

The dimensions of the wounds caused by burns and following necrectomy differ not only in both groups of animals but also dynamically during the course of the observation. The numerical values are shown in a graph (Figs. 4, 5).

In the third study setting, the presence of an allograft on the wound after necrectomy postponed the measurement of the length and breadth of the wound after the beginning of lysis and the rejection of the allograft. As a result, these values are only shown from the 14th day and all of them are statistically reliable.

The variations in the values for the dimensions of the wounds caused by burns are the result of the healing process and its progress in the dynamics of time. Another cause is the well-known contraction process (11). As the contraction is steady and unavoidable, it has to be accepted as a permanent feature in the spontaneous healing process. The coagulation necrosis after burns causes the rapid contraction of connective tissue fibres in the wound, its edges and the bordering zone. The following lysis of the necrosis and its fibres changes the elastic properties of the tissue. In addition, the skin of rats contains muscles which are fairly susceptible to irritating factors, trauma and affections. The same factors also change the conditions after total necrectomy in the second experimental setting.

The wound dimension values were studied separately and not only on the surface of the wound. The reason for this is the different direction and force of the contractibility of the elastic fibres and of the skin muscles in the different regions and segments of the skin of the rats (11). As a result, the length and breadth of the wound can change, even on some occasions when its total surface remains unchanged. An independent study of the length and breadth can determine the moment from which these dimensions start to decrease, not as a result of contraction but because of epithelialisation.

The dynamic study of the histological pictures reflects the development of the processes in the tissues at cellular level. The morphological results are reliable and, although they express everything descriptively and visually and not numerically and statistically, they are unambiguous.

The repair process in the burnt surface under a Mepitel dressing can be clearly seen on the 7th day in the formation of new granulating tissue. There are also significant numbers of endothelial cells and new vessels. The number of fibroblasts and mastocytes is also significant. At the edges of the wound, the initial regeneration of epithelium can be seen. In the underlying muscles, proliferation, resorption and macrophageal reaction are striking (Fig. 6).

These morphological phenomena are not seen in burn surfaces dressed with only cotton gauze before the 14th day (Fig. 7), i.e. 7 days later, and are less intensive. The demarcation line of leucocytes at the surface of the wound, which is infiltrated by Gram(+) cocci.

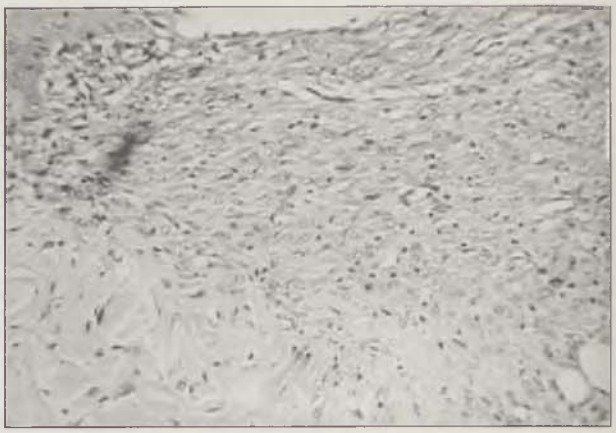

Fig. 6: The wound on the 7th day after the burn. The dressing is Mepitel. Magnification 10 x 6.3.

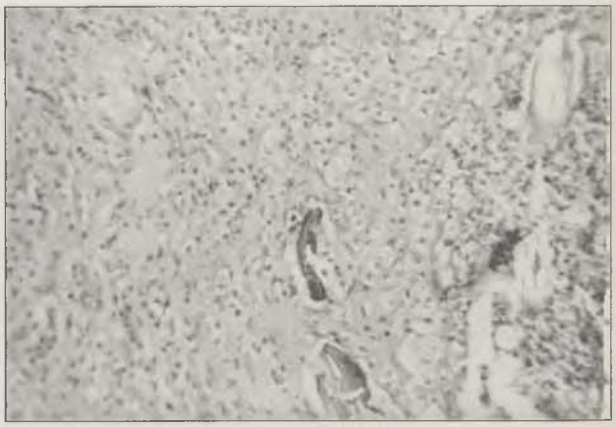

Fig. 7: The wound on the 14th day after the burn with a gauze bandage dressing. Magnification 10 x 6.3.

The healing processes develop in both groups until the end of the observation period, regardless of the differences in time.

The same picture is found at the wound and the surrounding skin after necrectomy (Figs. 8, 9).

The wound with an allograft following the necrectomy of the burnt skin begins to reject the allograft as early as the 3rd day. In the first

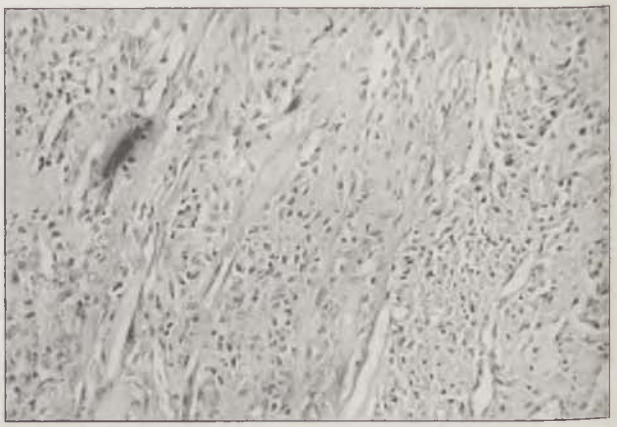

Fig. 8: The wound on the 7th day after the burn and necrectomy. The dressing is Mepitel. Magnification 10 x 6.3.

Fig. 9: The wound on the 14th day after the burn and necrectomy with a gauze bandage dressing. Magnification 10 x 6.3.

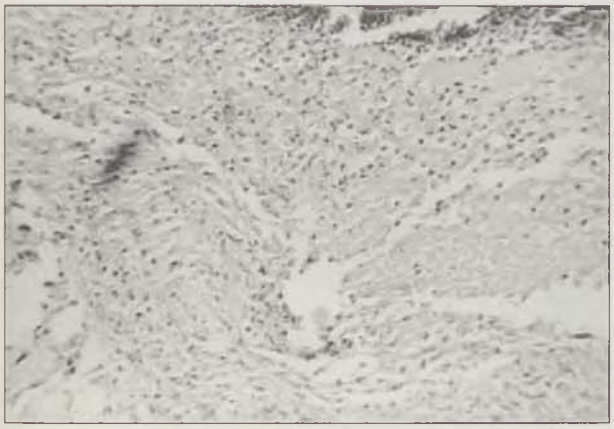

Fig. 10: The wound on the 3rd day after the burn, necrectomy and fresh full-thickness skin allograft. The dressing is Mepitel. Magnification 10 x 6.3.

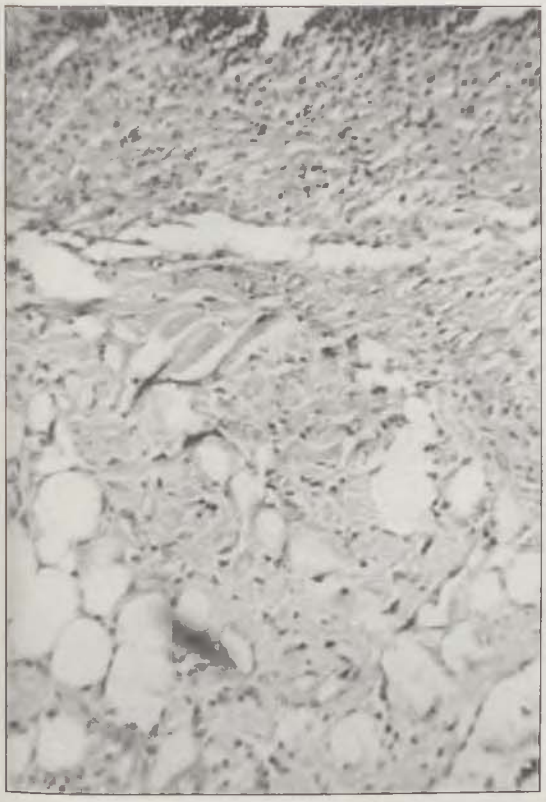

Fig. 11: The wound on the 3rd day after the burn, necrectomy and fresh full-thickness skin allograft with a gauze bandage dressing. Magnification 10 x 6.3.

group of animals, the reaction under the Mepitel dressing is far more violent, with phlemonous panniculitis (Figs. 10, 11). The proliferative reaction is present, although it is weaker, and appears in the same way as in the previous conditions and settings. In the second group, it appears on the 7th day, i.e. a delay of 4 days. The changes in the following conditions were as might have been expected, on the basis of the results in the first group.

DISCUSSION

Any study of new properties in the methods for the local treatment of burns has to be performed on the basis of an experimental model of this type, which guarantees repetition of the trauma and the conditions. This is the most important criterion if the results are to be reliable. In addition, a wound caused by heat provokes a number of morbid changes not only in the directly affected tissues but also in the skin surrounding the wound and this should be included in the observation. In our study, these two most important requirements have been strictly met on the basis of our long experience (15).

It is very important to note that the mortality rate during the first and second stages of the study is constant at 1.05% in the group of animals with a standard gauze dressing, whereas in the group of animals with Mepitel dressings not a single animal died. This drew our attention to the fact that Mepitel satisfactorily replaces the burnt or necrectomized skin. We can presume that Mepitel forms a suitable cover for the wound and favourably or beneficially supports the general reaction and the homeostasis in the organisms of the experimental animals after the heat trauma.

The equal trends in the microbial numbers demonstrate the similarity in the processes taking place in the wounds, independent of the significant difference in the three settings in this study. The fluctuations in the microbial numbers are influenced by the durability of the dressing, but this is unavoidable because of the character of the experimental animals. At the same time, we can conclude that Mepitel can be left on the wound for longer than other dressings.

The bacteriostatic properties of Mepitel are confirmed by the lasting reduction in the microbial numbers in the Mepitel treatment, with the preservation of the microbial species.

The changes in the dimensions of the wounds in the three study settings differ very little, but, at the same time, they show a lasting trend. Wound healing is a combination of two processes - contraction and epithelialisation. The contraction is evident at the start. It is characteristic that, under Mepitel, both the length and breadth of the wounds diminish more slowly

compared with the second group in the three settings. The most probable explanation is that conditions arise under Mepitel which impede and regulate the contraction. This process finishes on about the 20th day (4).

The reduction in both dimensions of the wounds begins after the 21st day and is faster under Mepitel. This is the process of epithelialisation (10).

After the removal of the dressing, the wound under Mepitel shows some preservation of moisture, although the perforations in the silicone evacuated the secretion towards the gauze above it (17, 18).

In our view, Mepitel creates suitable conditions and regulates the development of the normal biological processes and condition of the tissues to enable the wounds to heal.

In both groups of animals, the histological picture of the development of the wounds and the skin surrounding them reveals the same tendency in every experimental setting. The tissue restitution processes under Mepitel appear and develop 3-7 days earlier.

In the third study setting, this presents itself in the form of a faster and more violent reaction involving the rejection of the allograft.

The more rapid changes in the connective tissue and particularly the widening of the regenerating epithelium during the last few days of the observation period are in agreement with the changes in the dimensions of the wounds.

CONCLUSION

We find that the experimental method for investigating burns and their surrounding skin is suitable for this and other similar studies because it offers an opportunity for repetition and the comparative analysis of the results. The method permits observations in experimental conditions of the local treatment methods used in clinical practice.

When applied immediately to a burn, Mepitel prevents contamination as its perforations drain the secretions. The bacterial flora is limited in its development, probably as a result of the chemical structure of the material (1, 2, 12).

Mepitel creates the conditions for the more rapid rejection of skin allografts. It accelerates and regulates normal biological healing processes.

DEDUCTION

When applied immediately after the trauma to a burn, Mepitel demonstrates bacteriostatic properties, which enable it to be changed after an extended period of time.

Mepitel activates the normal healing processes in the wound and surrounding zone by accelerating and regulating them.

Mepitel is not suitable as a dressing on skin allografts because it stimulates the rejection reaction.

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Hypertrofické jizvy a keloidy: revize vracejícího se problému

V. Ellitsgaard, N. Ellitsgaard

Nadměrné jizvení způsobené patologicky přebujelými kolagenními depozity je problém známý všem chirurgům. Takové komplikace při hojení ran, známé jako hypertrofické jizvy a keloidy se mohou stát esteticky nepřijatelnými pro pacienta a některé jizvy mohou dokonce způsobit anatomickou dysfunkci.

V přehledu literatury o plánování a strategii léčby shromáždili chirurgové ohromující množství hypotéz na toto téma. Zdá se však, že neexistuje žádný absolutně efektivní způsob léčby hypertrofických jizev a keloidů a počet léčebných způsobů ilustruje nedostatek znalostí týkajících se tohoto způsobu patologického jizevnatého hojení. Většina studií nebyla dobře řízena, což přineslo rozporné výsledky.

Tento přehled načrtl podstatu hypertrofických jizev a keloidů. Je založený na kritickém hodnocení léčebných způsobů a je vodítkem pro výběr léčby, je-li předpokládána.

Syndrom karpálního tunelu: Revize motorické thenarové větve?

J. Drápela, J. Syrový, M. Kulakovská

Autoři ve svém sdělení prezentují své názory a zkušenosti z operací syndromu karpálního tunelu (KT). Pro multifaktoriální etiologii onemocnění nemohou doporučit schematické řešení uplatňující jeden operační postup pro terapii všech případů. Především při operaci je nutno řídit se lokálním nálezem, podpořeným nálezem neurologickým. Rozbor jednotlivých operačních kroků a jejich diskuse je provedena právě se zřetelem na jejich rizika a je diskutován i přínos z hlediska kauzality řešení. Autoři doporučují revizi thenarové větve nervi mediani.

V období 1/1994 - 10/1996 bylo sledováno 212 případů. Předoperačně ve 100 % provedeno EMG a v celkovém zhodnocení nalezen v 94 % dobrý pooperační výsledek.

Změny kraniofaciálního růstu a vývoje u mužů s úplným jednostranným rozštěpem rtu a patra ve věku od 5 do 20 let

M. Drahorádová, Ž. Müllerová, Z. Šmahel

Práce je založena na antropometrickém vyhodnocování telerentgenových snímků dvou souborů mužů s úplným jednostranným rozštěpem rtu a patra. První soubor byl vyšetřen v 5, 10 a 15 letech, druhý v 15 a 20 letech. Snímky byly hodnoceny pomocí Jarabakovy analýzy. Cílem bylo srovnání velikosti růstu a charakteru vývojových změn v předpubertálním, pubertálním a postpubertálním období života. Růstová rychlost skeletálních struktur byla největší v předpubertálním období, o málo menší v pubertálním období a v menší míře růst přetrvával i v období postpubertálním. Vysoká růstová rychlost v předpubertálním období souvisí patrně s prořezáním zubů trvalého chrupu. I přes výrazné zhoršení vertikálních a sagitálních mezičelistních vztahů, ke kterému dochází v předpubertálním období, se v průběhu tohoto období podařilo slabě zlepšit skus ve frontální krajině chrupu, během puberty a v postpubertálním období k dalšímu zlepšení již nedošlo. Výsledky odpovídají faciálnímu typu růstu s poměrně nevýrazným pubertálním spurtem.

Antropometrické charakteristiky obličeje kojenců s oboustranným rozštěpem rtu a patra

B. Antoszewski, J. Kruk-Jeromin

Antropometricky byl před operací rtu vyšetřen obličej 21 kojenců ve věku 6 - 9 měsíců (15 chlapců a 9 dívek) s oboustranným rozštěpem rtu, čelisti a patra. Kontrolní soubor tvořilo 30 zdravých jedinců. U dětí s oboustranným rozštěpem rtu a patra byl prokázán nedostatečný vývoj horní a dolní čelisti a zvětšení šířky nosu.

Rozdíl v embryotoxicitě vitaminu A a B-karotenu zjištěný u kuřecího zárodku metodou CHEST

M. Peterka, R. Peterková, Z. Likovský

Teratogenní účinek vitaminu A byl objeven u laboratorních savců již v roce 1953. Téměř o 30 let později byla zjištěna teratogenicita analogu vitaminu A - isotretinoinu u člověka. U 25 % novorozenců exponovaných během prvního trimestru těhotenství vyvolával isotretinoin těžké vrozené vady kraniofaciální oblasti a centrálního nervového systému, kardiovaskulární vady a vady thymu. Biologická konverze isotretinoinu na vitamin A je obecně známá. Proto se epidemiologické studie zaměřily na těhotenství matek, které užívaly vitamin A ve vysokých dávkách. Matky, které užívaly denně vitamin A během časných fází těhotenství měly dvakrát vyšší riziko, že se jim narodí dítě s vrozenou vadou. Proto bylo doporučeno nahradit vitamin A jeho přírodním prekurzorem B-karotenem, u kterého se předpokládá, že je mnohem bezpečnější pro těhotné ženy díky omezenému vstřebávání ze střeva. Cílem naší studie bylo otestovat možný přímý účinek B-karotenu u kuřecího zárodku a porovnat výsledky se známou embryotoxicitou vitaminu A na stejném experimentálním modelu. Pro odhad začátku pásma embryotoxicity (tj. pro určení minimálních embryotoxických dávek vitaminu A a B-karotenu) bylo použito subgerminální nebo intraamniální injekce zárodkům kuřete ve stáří 2.-5. embryonální den. Vitamin A začal narušovat vývoj zárodku v rozmezí dávek 0,3 - 0,03 mmmg. Byly zjištěny malformace hlavy, končetin a srdce - podobně jako tomu bylo u laboratorních savců a u člověka. B-karoten nepoškozoval zárodky ani v nejvyšších testovaných dávkách - 100 mmmg. Výsledky dokumentují velký rozdíl mezi přímou embryotoxicitou vitaminu A a B-karotenu. Po teoretické extrapolaci výsledků získaných na zárodku kuřete, jsme odhadli minimální embryotoxické dávky vitaminu A pro savce mezi 0,1 - 1 mg/kg váhy matky a B-karotenu vyšší než 1000 mg/kg váhy matky. Epidemiologické studie prokázaly teratogenitu vitaminu A u člověka po denních terapeutických dávkách 25 000 IU - 8,3 mg (0,13 mg/kg) a bylo doporučeno neužívat vitamin A v denních dávkách větších než 10 000 IU (0,05 mg/kg). Naše výsledky o teratogenitě vitaminu A získané na kuřeti jsou v souladu s tímto doporučením. Přívod vitaminu A v potravinách je v běžné české populaci pro těhotnou ženu dostatečný, a proto podávání vitaminu A v lékové formě nese riziko předávkování. Naše výsledky rovněž potvrzují názor, že v případech, kdy je třeba podávat vitamin A v těhotenství, je lépe jej nahradit B-karotenem.

Bakteriostatický a biologický stimulující efekt obvazu s Mepitelem na experimentální popáleninu kůže krys

K. Troshev, Z. Kolev, A. Zlateva, S. Shishkov, N. Pashaliev, E. Raycheva-Mutafova

Tato studie byla provedena u 200 bílých krys „Wistar", z nichž každá vážila okolo 200 gr. Zvířata byla rozdělena do dvou skupin, u první skupiny byla rána obvázána obvazy s Mepitelem, v kontrolní skupině pouze bavlněnými obvazy. Mikrobiologické a histologické vyšetření a měření rány bylo provedeno 3., 4., 14., 21. a 28. den po způsobení popáleniny 3. stupně standardní metodou. Pozorování zahrnuje popáleniny se standardním vylučováním nekróz a hojení ran po operativní totální nekrektomii popálené kůže a spontánním hojení a popáleniny s totální operativní nekrektomií s následným štěpováním s allotransplantáty.

Kvantitativní výsledky prokazují statisticky spolehlivou bakteriostatickou aktivitu přes i pod obvazy s Mepitelem. Histologický obraz ilustruje značnou aktivitu tkání pod Mepitelem. Projevuje se to zrychlením hojivého procesu v ranách po popáleninách po nekrektomii spálené kůže. Mepitel na allotransplantátu v ráně po nekrektomii spálené kůže provokuje včasnou a rychlou eliminaci štěpu. Biologická aktivita Mepitelu byla také potvrzena statisticky spolehlivými daty v dynamických změnách v délce a šířce ran.

Autoři uzavírají, že Mepitel aplikovaný bezprostředně na popáleninu nebo ránu po nekrektomii popálené kůže potlačuje rozvoj mikrobiální flory a stimuluje hojivý proces. Mepitel není vhodný pro obvazy allotransplantátů, neboť silně urychluje jejich vyloučení (odmítnutí).

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