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CASE REPORT
KAZUISTIKA

Deep Venous Thrombosis after Conservative Treatment of Clavicular Fracture in COVID-19 Negative Children: Two Case Reports

Hluboká žilní trombóza po konzervativní léčbě klavikulárních zlomenin u Covid-19 negativních dětí: dvě kazuistiky

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SUMMARY

A 13-year-old girl suffered fracture of her left clavicle. A figure-of-8 bandage was placed during initial treatment. Six days after trauma her distal arm, elbow and proximal forearm were swollen, pain and tenderness of distal part of brachial vein was recognized during clinical examination. Duplex ultrasonography revealed partial thrombosis of the brachial vein. Bandage was immediately removed and administration of LMWH (enoxaparin) was started. Complete recanalization was achieved after a few days. The fracture was healed without further complication, patient was without sonographic and clinical signs of post-thrombotic syndrome. The second case report describes a 14-year-old boy. Initially, the fixation was a figure-of-8 bandage. 5 days after the injury he had swollen arm and elbow on the injured side, according to duplex ultrasonography deep venous thrombosis of the axillary and the brachial vein was recognized. There was only partial recanalization at the first sonographic follow up, the patient was converted to Warfarin for 3 months after injury after initial LMWH therapy. At the last follow-up, fracture of the left clavicle was healed and there were no DUSG or clinical signs of post-thrombotic syndrome.

Key words: clavicle, deep venous thrombosis of the upper extremity, anticoagulant therapy.

CASE REPORT 1

A 13-year-old girl was injured her left shoulder during performing a handstand. She was treated on the day of injury, fracture of the middle 1/3 of the left clavicle was diagnosed, a figure-of-8 bandage was used. She was without peripheral neurological or vascular deficiency (Fig. 1). 6 days after injury, her mother observed progressive swelling of the left arm and the proximal half of the forearm. The arm, the elbow and proximal half of the forearm were oedematous, but without noticeable over-compression of the figure-of-8 bandage. The fracture was in good position on follow up radiograph. The limb circumference was 28 cm above the elbow and 27 cm below the elbow, while on the right side only 23.5 cm at both locations. Palpation pain and tenderness was above the distal ½ in the medial surface of the arm. Duplex ultrasonography was performed: the brachial vein was not fully compressible, Doppler curve revealed slowing of the venous flow, partial thrombosis was assessed in the middle third of the arm, the subclavian and the axillary vein and deep forearm veins were without evidence of thrombosis (Fig. 2). The clavicular bandage was removed immediately and the elbow was left in the sling. The level of D-dimers was very high (0.69 mg /l, laboratory reference 0.16–0.39 mg/l).

The patient was admitted at the paediatric department, where full anticoagulant therapy (enoxaparin 0.4 ml s.c. twice daily with antiXa controls) was initiated.

The nasopharyngeal swab sample for RT-PCR testing of COVID-19 was negative.

After the beginning of anticoagulant therapy the clinical symptoms were rapidly improved - after 3 days there was a significant regression of oedema and complete disappearance of palpation pain in the arm. At the sonography, 3 days after initiation of anticoagulant therapy, complete recanalization was observed in the brachial vein (Fig. 3). LMWH was reduced to higher prophylactic dosage – enoxaparin 0.4 ml s.c. a day. There was no history of thromboembolic disease or thrombophilia in the patient or her parents, she had not received any hormonal contraception, she had been non-smoker, and there had been no recent intravenous drugs administration, or intravenous catheters. Activity of coagulation factors were normal. The patient was released in general good state after 5 days. 3 weeks after injury the fracture was healing in a good position, she was without signs of a post-thrombotic syndrome. She was free of complaints at 6-week follow-up at the paediatric haematologist.

CASE REPORT 2

A 14-year-old boy was injured his left shoulder while he was playing ice hockey and hit on a cushion, suffered a fracture of the middle third of the clavicle. He was COVID-19 negative (according RT-PCR nasopharyngeal swab test). Fracture was fixed by a figure-of -8 bandage.

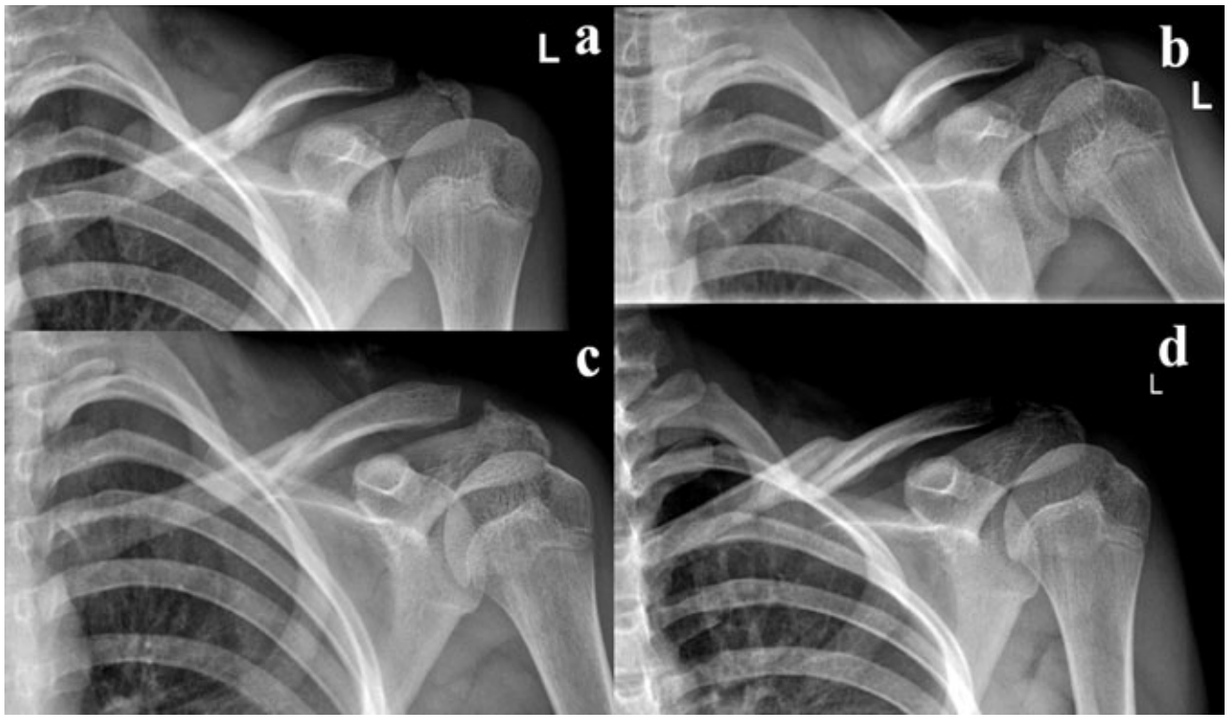

Fig. 1. Plain radiograph in AP view: 1a – initial traumatic X-ray, 1b – after figure 8 bandage, 1c – follow up X-ray scan during diagnosis of the brachial deep venous thrombosis, 1d – after fracture healing.

The fracture position was satisfactory on X-ray scan (Fig. 4). 5 days after injury, he complained swelling of his left arm, diffuse oedema, palpation pain and tenderness was recognized, left arm circumference was 33 cm (right one 31 cm only). The patient was free of neurovascular deficit. Bypassed thrombosis at the level of the axillary vein was revealed during duplex ultrasonography, thrombosis was extended to the proximal half of the brachial vein and to the basilic vein, superficial veins were slightly dilated (Fig. 5). D-dimers were significantly increased to 1.85 mg / l (reference value for given age 0.16–0.39). VIII activity was elevated to 170% (normal lab values 50-150%). Bandage was removed and fixation was changed to Dessault brace. Patient was admitted for further therapy at the paediatric department, where LMWH administration at therapeutic dosage (enoxaparin 0.8 ml twice daily with anti-Xa con-

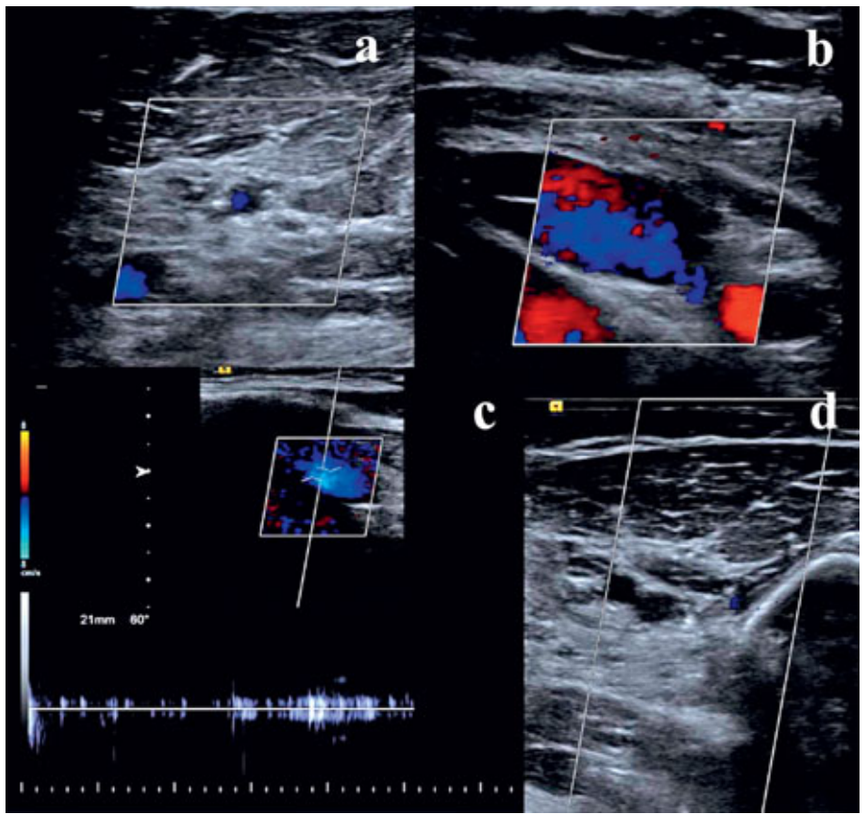

Fig. 2. Duplex ultrasonography of deep veins of the left upper extremity, partial thrombosis of the brachial vein is imaged; upward images show the subclavian vein, downward the not fully compressible brachial vein is shown.

trols) was initiated by the paediatric haematologist. 9 days after injury, thrombosis was persistent at the proximal fourth of the brachial vein, while the axillary and subclavian veins were recanalized. The patient was therefore converted to Warfarin and diminished on day 5 of hospitalization.

Complete recanalization of the brachial vein was achieved after one month (Fig. 6).

Anticoagulation therapy was finished 3 months after injury. The fracture of the clavicle was healed, the patient was free of sonographic as well as clinical signs of post-thrombotic syndrome. Patient was without thrombophilia according to the genetic examination. Activity of all coagulation factors was normal at the last follow up.

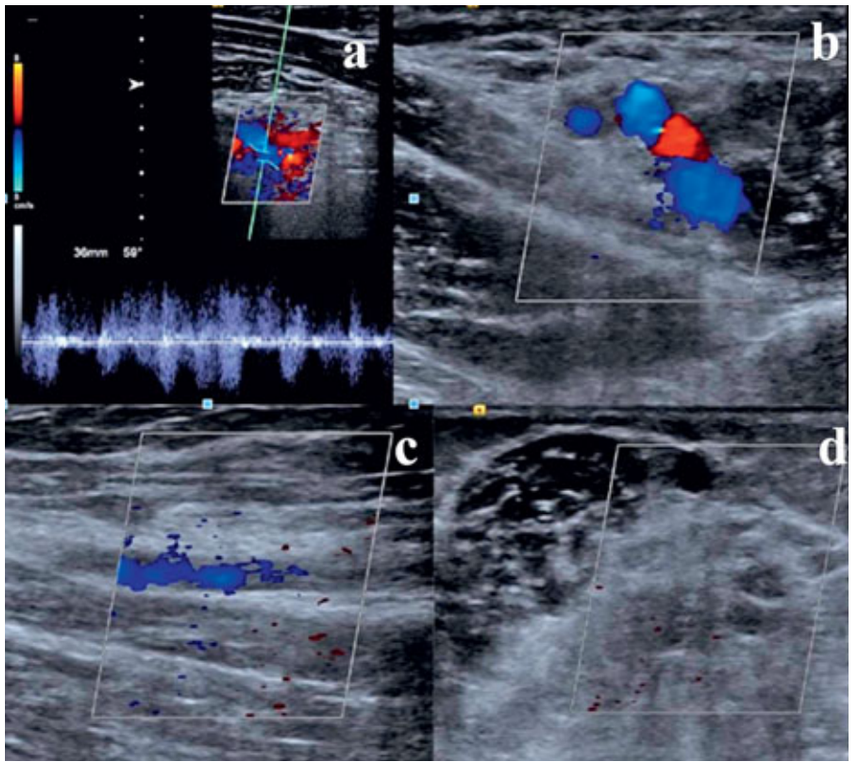

Fig. 3. Duplex ultrasonography after successful treatment with LMWH – the brachial vein was completely recanalised, the venous flow was normal, the brachial vein was fully compressible.

DISCUSSION

Both conservative and surgical treatment of clavicular fracture can be complicated by deep venous thrombosis (DVT). The estimated incidence of upper extremity DVT in children is 0.4 to 1 per 100,000 patients (10–15). DVT in the upper limbs can be distinguished by 2 categories: primary and secondary (12). Primary (idiopathic, unprovoked) DVT is a form of venous occlusion where no acquired or externally acting risk factors can be demonstrated. It

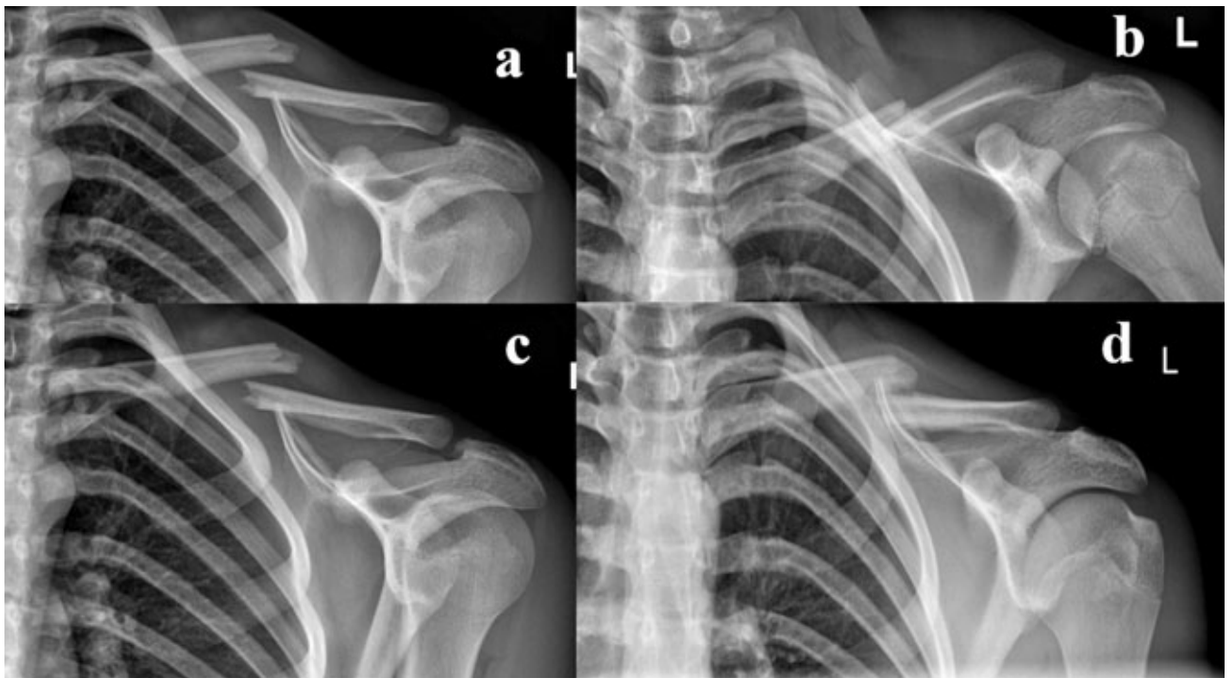

Fig. 4. Plain radiograph in AP view: 4a – initial traumatic X-ray, 4b – after figure-of-8 bandage, 4c – follow up X-ray scan during diagnosis of the brachial deep venous thrombosis, 4d – after fracture healing.

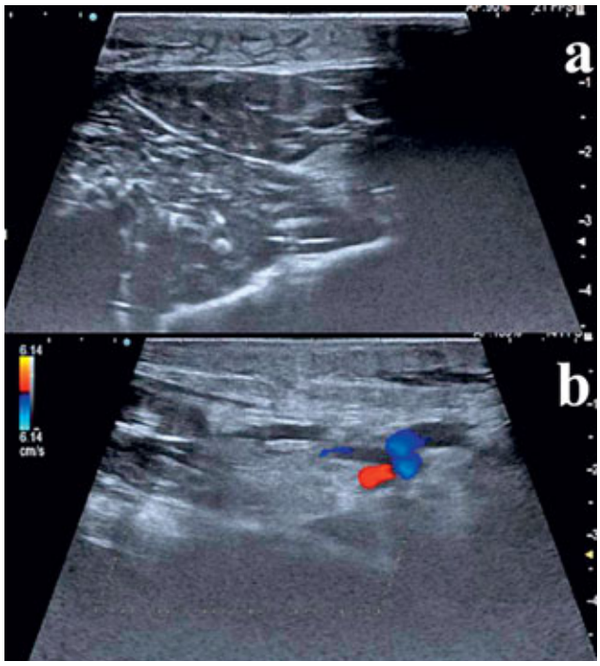

Fig. 5. Duplex ultrasonography of deep veins of the left upper extremity, thrombosis of the axillary and the brachial vein are diagnosed.

represents approximately 20% DVT, most often associated with congenital thrombophilia or vascular thoracic outlet syndrome (anatomical narrowing due to the cervical rib, variation of subclavian muscle, aneurysmatic dilatation of the subclavian vein; a combination of these factors). The vascular thoracic outlet syndrome can be also associated with acute limb ischaemia or subclavian steal syndrome (1–3, 6, 7, 8, 10, 12, 13).

Secondary (provoked) DVT is more common (about 80%), develops as a result of risk factors. Compression of vessels can be directly by displaced clavicular fragment, haematoma, vascular spasm, fixation may be involved in compression - especially the figure-of-8 bandage (brace, Delbet rings) may slow the venous flow from the deep veins of both the arm and axilla, in addition to limiting venous blood flow, an excessively tight bandage can cause secondary lymphoedema (9, 13).

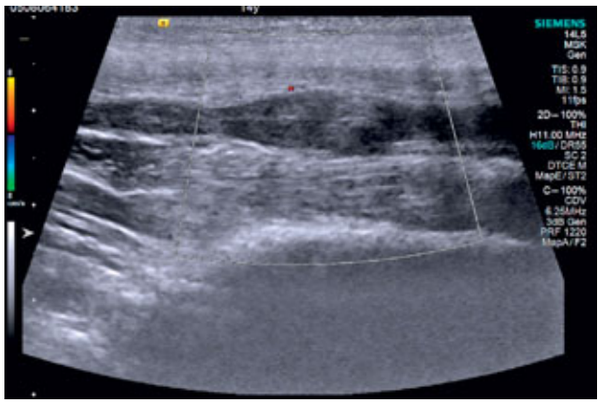

Fig. 6. Complete recanalization after one month.

Fracture are a rare cause of DVT in the upper extremity area, in adults approximately 2% of DVT of the subclavian or the axillary vein are associated with clavicular fracture (9). A more frequent cause is secondary DVT with the inserted central venous catheter (11), peripherally inserted central catheter (PICC), primary and secondary expansion processes. Provoked DVT can be also associated with intrinsic risk factors – hormonal contraception, pregnancy, peripartum period, oncological and haemato-oncological diseases, progression of superficial thrombophlebitis.

Muscle injuries with oedema or excessive muscular load in the forced position (effort induced DVT, Paget-Schroetter syndrome) also contribute to risk of DVT (especially prolonged load in hyperabduction of the upper limb for the subclavian and axillary DVT – e.g. in baseball players). Carrying of loads by shoulder straps, plaster fixation of the forearm or elbow (especially in patients with primary thrombophilia) are also associated with a higher risk of upper limb DVT (8).

Clinical examination, duplex ultrasonography of the venous system and elevation of D-dimers are used for diagnosis of upper limb deep venous thrombosis (9–14). Up to 50% of patients can be asymptomatic. The most common symptom is oedema, which can be confirmed by measuring the circumference of the limb - in case of the brachial vein, the circumference above the elbow and below the elbow is measured to compare with the uninjured limb. Another symptom is palpation pain - it may be close to the occlusion, but there may be irradiated pain (at axillary and subclavian DVT) of the neck, posterior surface of the shoulder. Dilatation of superficial veins on the anterior surface of the shoulder, in the axilla, on the anterior surface of the chest – mainly in the pectoral region – is accompanied rather with complete occlusion of the subclavian vein, in the early period may not be noticeable. Palpation pain in the vicinity of the brachial vein (palpation tenderness of the medial bicipital groove) was also observed in our patients (9). In case of subclavian vascular bundle compression, acute limb ischaemia (poor palpable pulsation, paleness, decreased skin temperature, suddenly increased pain, peripheral paraesthesia, peripheral movement disorder, peripheral sensitivity dysfunction) may also be signs of vascular thoracic outlet syndrome, in case of suspicion of possible limb ischaemia, examination by a vascular surgeon is emergently required (3–7, 9).

Duplex ultrasonography of veins (DUSG) is the gold standard of DVT imaging and assessment. DUSG examinations include vein compressibility, peripheral augmentation, venous flow measurement (Doppler flow curve, assessment of venous inflow and outflow), the extent of thrombotic occlusion, also post-thrombotic changes could be revealed by DUSG (e.g. residual thrombus, mural venous changes, intraluminal bridges, venous hypertension). The first patient experienced rapid and complete recanalization after initial anticoagulant therapy, but the second patient was recanalized after one month. In the event that DUSG is not valid; there is no clear extent of thrombosis, MRI angiography is added

(13). Only in case of planned intervention in the deep veins digital subtraction venography is performed (3).

D-dimers should be very high in acute deep venous thrombosis (it is necessary to assess the level according to the reference range for patient's age); in case of negative value of D-dimers acute venous thrombosis is very improbable. Our patients had very high D-dimers, confirming acute DVT.

Anticoagulant therapy has been implicated in DVT management (9–15). In children, low molecular weight heparins are most commonly used, dosage is always based on the recommendation of a paediatric haematologist and controlled by antiXa levels. Anticoagulant therapy after recanalization should be maintained for the entire duration of reduced mobility of the injured upper limb (at least 4 weeks after injury), in case of proved thrombophilia or in case of delayed recanalization, the therapy is switched to oral anticoagulants within 3 months of injury (9).

Alternative anticoagulants are required, if allergy to LMWH is present, or there is anamnestic record of heparin-induced thrombocytopenia. Alternative anticoagulant therapy is always controlled by the paediatric haematologist, in adolescents it is possible to use fondaparinux under antiXa (fondaparinux) controls, DOACs – rivaroxaban, dabigatran can be also used[1]).

The figure-of-8 bandage should be removed as soon as the DVT is suspected, the injured limb is left on the sling in children over 3 years of age. In case of failure of anticoagulant therapy, in case of DVT progression, in the development of complicated acute limb ischaemia, an interventional therapy is indicated – venography + thrombectomy, event. with local thrombolysis. In case of contraindication of venography (e.g. in case of the gracile, small lumen vein) open revision by the vascular surgeon and thrombectomy are indicated. In complicated ischaemia, the arteries are also revised, in some cases decompression of the subclavian vascular bundle can be beneficial (3, 9).

In differential diagnosis it is necessary to distinguish primary DVT of the upper limb (history of thrombophilia, positive family history of thromboembolic disease), oedema at primary or secondary antiphospholipid syndrome (APLA investigation – anti-cardiolipin antibodies; IgG and IgM beta-2 glycoprotein-1 antibodies) (6), primary lymphoedema, primary angiooedema (C1 inhibitor deficit), allergic (secondary) angiooedema (e.g. after insect sting, drug induced – ACE inhibitors). Acute limb ischaemia of non-traumatic etiology, vasculitis (often other skin changes, in children Henoch-Schönlein purpura – skin purpura, renal involvement, Kawasaki syn. – skin and mucosal changes, risk of coronary artery lesions), superficial thrombophlebitis, 1erysipelas and other phlegmonous infections of soft tissues, other infections associated with lymphadenitis and lymphangitis are included in differential diagnosis. However, heparin-induced thrombocytopenia type 2 (thrombocytopenia and heparin administration) can also be cause of DVT in the upper limb (10). Recently has been reported COVID-19 associated upper limb thrombosis in children (16). This is fully different type of paediatric DVT, risk factors of DVT in COVID-19 include: age ≥12 years, oncological treatment, presence of a central venous catheter and multisystem inflammatory syndrome in children (16). The most common anticoagulant in treatment of this type DVT was enoxaparin, administered twice daily and controlled by 4-hour postdose anti-Xa levels (16). Until now, we have no clinical experience of COVID-19 associated DVT in children at our department.

Although up to 33% of complicated pulmonary embolism can be imaged, only about 5% of patients are symptomatic (10). The risk of complicated pulmonary embolism increases especially in late and inappropriate treatment. With early therapy, the prognosis is good and paediatric patients have a very low risk of development of post-thrombotic syndrome after provoked DVT (1, 11, 13, 15), which is contrary to primary DVT (where at least moderate grade post-thrombotic syndrome is common). Prevention of DVT is regular follow up of all treated patients to prevent distress fixation and administration of LMWH throughout the fixation period, reduced mobility of the shoulder respectively in patients at risk – optimal 4-hour postdose anti-Xa level is 0.20 to 0.49 IU/ml (16).

Both cases of described DVT occurred in the fall of 2020. The estimated incidence of DVTs with clavicle fracture in 2020 was 1.2 per 100 000 children per year (two patients at Department of Paediatrics). 8 patients (5 boys and 3 girls) were addressed to clavicle stabilization during this year (clavicular plates 3, ESIN 2, K wires 2 and a figure-of-eight cerclage once) during 2020, the mean age was 12,7 ± 4.1 years 95% CI (9.8–14.8), no DVTs was observed in .surgically treated group. We can't therefore provide clear guideline or recommendation for surgical treatment due to the relatively low counts of surgically treated children with clavicle fracture together with extremely low incidence of complicated DVTs. In case of post-traumatic DVT and subclavian vascular bundle compression, cooperation with paediatric vascular surgeon, interventional radiologist and paediatric haematologist is required.

CONCLUSIONS

Deep venous thrombosis after clavicular fracture is extremely rare in children. Diagnosis is based on a com-

[1] **Rivaroxaban (Xarelto 1 mg/ml)** is indicated for treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in full-term neonates, infants and toddlers, children and adolescents aged less than 18 **years after at least 5 days of initial parenteral anticoagulation**. For children weighing 12 to 30 kg, the dosage is 5 mg (=5 ml) twice a day, for children weighing 31 to 50 kg, the dosage is 15 mg (=15 ml) once a day. For children up to 12 kg, it is given 3 times a day according to the current weight and recommendations in spc. **Dabigatran (Pradaxa** 20 mg coated granules for toddlers and children and Pradaxa 6.25 mg/ml up to 1 year of age) can be also used, the dosage is twice a day according the body weight and age spc recommendations **after at least 5 days of initial parenteral anticoagulation**.

bination of clinical examination and duplex ultrasonography of the veins. In addition to releasing fixation, anticoagulant therapy is included in the therapy. In known thrombophilia, thromboprophylaxis is indicated during fixation by a figure-of-8 bandage even in paediatric patients.

Abbreviations
ACE – angiotensin converting enzyme
APLA – antiphospholipid antibodies
C1 – inhibitor – protease inhibitor of C1 (it prevents spontaneous activation of classical pathway of complement due to inhibiting C1s and C1r proteases)
DOAC – direct oral anticoagulant
DUSG – duplex ultrasonography
DVT – deep venous thrombosis
LMWH – low molecular weight heparin
PICC – peripherally inserted central (venous) catheter
spc – summary of product content

Ethical standard statement
Our study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent (signed by both parents) had been gain prior publication.

Conflict of interest
All authors declared no conflict of interest.

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