

IMPACT OF THE CD40-CD40L SYSTEM ON PAIN INTENSITY IN CHILDREN AFTER ANTERIOR ABDOMINAL WALL SURGERY USING VARIOUS ANAESTHESIA TECHNIQUES

Vplyv CD40-CD40L na intenzitu bolesti u detí po operácii prednej brušnej steny s použitím rôznych techník anestézie

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Abstract

Background. The aim of the study was to assess changes in the serum CD40L level and its potential relationship with pain intensity in children after anterior abdominal wall surgery on the background of general anaesthesia and its combination with various RA techniques.

Materials and methods. The study included 87 children who underwent anterior abdominal wall surgery using different analgesic techniques. All children were divided into 3 groups: Group I - 33 children - general anaesthesia using morphine; Group II - 27 children - general anaesthesia using the transversalis fascia plane block (TFPB); Group III - 27 children - general anaesthesia using the TFPB, combined with the quadratus lumborum block 4 (QLB-4) via a single injection.

Results. In Group I, 2 hours after surgery, the mean serum level of CD40L was 4.283 pg/ml, with a slight downward trend at discharge ($U_{\text{Mann-Whitney}} = 52.5$; $p = 0.593$). In Group II, the level of CD40L reduced significantly by 25.3% ($U_{\text{Mann-Whitney}} = 10.0$; $p = 0.002$); 24 hours after surgery, the level of CD40L reduced by 15.1% ($U_{\text{Mann-Whitney}} = 26.0$; $p = 0.20$). At discharge, the level of CD40L in this group reduced significantly by 54.4% ($U_{\text{Mann-Whitney}} = 7.0$; $p = 0.003$). In Group III, during all observation periods, the mean serum level of CD40L was 4 - 7.6 times lower ($U_{\text{Mann-Whitney}} = 0.0$; $p = 0.000$) than corresponding levels in children of Group II.

Conclusion. The indicators of CD40L signalling were found to increase in paediatric anterior abdominal wall surgeries. There was a close positive correlation between postsurgical pain intensity and CD40L serum levels. Single-injection TFPB+QLB-4 resulted in the lowest serum CD40L levels, an indicative of the lowest intensity of postsurgical pain.

Clinical Trial registration. The study is a fragment of the research project "Health Status and Adaption of Children from the Precarpathian Region with Somatic Diseases, Their Prevention" 2021 - 2026, state registration number 0121U111129 (Ivano-Frankivsk National Medical University) (Tab. 2, Ref. 30). Text in PDF www.lekarsky.herba.sk.

KEY WORDS: regional analgesia, CD40L, postsurgical pain, children, pain management.
Lek Obz 2024, 73 (3): 91-95

Abstrakt

Cieľom štúdie bolo posúdiť zmeny sérovej koncentrácie CD40L a jej potenciálny vzťah k intenzite bolesti u detí po operácii prednej brušnej steny počas celkovej anestézie a jej kombinácie s rôznymi technikami regionálnej anestézie.

Materiály a metódy. Do štúdie bolo zaradených 87 detí, ktoré podstúpili operáciu prednej brušnej steny rôznymi analgetickými technikami. Všetky deti boli rozdelené do 3 skupín: *Skupina I* - 33 detí - celková anestézia s použitím morfia; *Skupina II* - 27 detí - celková anestézia s použitím transversalis fascia plane block (TFPB); *Skupina III* - 27 detí - celková anestézia s použitím TFPB, kombinovaná s quadratus lumborum block 4 (QLB-4) prostredníctvom jednej injekcie.

Výsledky. V 1. skupine bola sérová koncentrácia CD40L 2 hodiny po operácii priemerná - 4,283 pg/ml, s miernym klesajúcim trendom pri prepustení ($U_{\text{Mann-Whitney}} = 52,5$; $p = 0,593$). V 2. skupine sa hladina CD40L významne znížila o 25,3 % ($U_{\text{Mann-Whitney}} = 10,0$; $r = 0,002$); 24 hodín po operácii sa koncentrácia CD40L znížila o 15,1 % ($U_{\text{Mann-Whitney}} = 26,0$; $p = 0,20$). Pri prepustení zaregistrované jej významné zníženie o 54,4 % ($U_{\text{Mann-Whitney}} = 7,0$; $p = 0,003$). V 3. skupine bola počas všetkých období pozorovania priemerná sérová koncentrácia CD40L - 4 - 7,6-krát nižšia ($U_{\text{Mann-Whitney}} = 0,0$; $p = 0,000$) ako zodpovedajúce koncentrácie u detí z 2. skupiny.

Záver. Zistilo sa, že indikátory signalizácie CD40L sa zvyšujú pri chirurgických výkonoch na prednej brušnej stene u detí. Medzi intenzitou pooperačnej bolesti a sérovou koncentráciou CD40L bola úzka pozitívna korelácia. Použitie kombinácie TFPB+QLB-4 malo lepší efekt a viedlo k primeraným koncentráciám CD40L v sére, čo svedčí o najnižšej intenzite pooperačnej bolesti.

Registrácia klinickej štúdie. Štúdia je fragmentom výskumného projektu „Zdravotný stav a adaptácia detí z Predkarpatskej oblasti so somatickými ochoreniami a ich prevencia“ 2021-2026, štátne registračné číslo 0121U111129 (Ivano-Frankivsk National Medical University) (Tab. 2, Ref. 30). Text v PDF www.lekarsky.herba.sk.

KLÚČOVÉ SLOVÁ: regionálna analgézia, CD40L, pooperačná bolesť, deti, manažment bolesti.
Lek Obz 2024, 73 (3): 91-95

Introduction

The CD40-CD40L system, which is involved in the regulation of immunological processes, including T cell activation, immunoglobulin and cytokine production, has recently attracted increasing attention. Impaired CD40 signaling is involved in the pathogenesis of many pathological processes associated with the development of the inflammatory response and thrombosis (3, 28).

CD40 and CD40 ligand (CD40L) are known as type I and type II transmembrane proteins belonging to the tumor necrosis factor (TNF) superfamily, which exist in both membrane-bound and soluble forms. CD40 is expressed on both immune (B cells, dendritic cells, monocytes, and macrophages) and non-immune cells (endothelial cells, vascular smooth muscle cells, and fibroblasts). In the central nervous system, CD40 is expressed by microglia, while neurons and astrocytes are not capable of producing this protein. CD40L is mainly expressed on activated T cells and platelets in response to infectious and non-infectious inflammatory processes. If CD40L interacts with CD40 receptor, trimerization of the latter occurs, which leads to its activation. The activation of CD40 receptor stimulates the secretion of growth factors, chemokines, and pro-inflammatory cytokines through a variety of intracellular signal transduction pathways (3, 23).

Experimental models for the study of peripheral nerve damage have demonstrated that the CD40-CD40L pathway is involved in the generation of neuropathic pain (1, 4, 12) associated with increased expression of chemokine (CCL2) and calcitonin gene-related peptide (CGRP) (16, 19, 21).

However, literature data on the pronociceptive effects of the CD40-CD40L pathway are scarce and its role in pain generation in practical medicine, especially anaesthetic practice, has not been studied at all. Pain is one of the earliest psychophysical functions to be formed; by the 30th week of pregnancy, all the pathways of pain transduction and perception are already formed; thus, both fetus and child are able to perceive pain and its intensity is often even greater than in adults. Some experts erroneously believe that infants do not feel pain as their central nervous system is still immature (13). Abdominal pain is an important adaptive response of the body which sends an alarm signal in response to harmful stimuli and enables us to choose the most appropriate behaviour for the situation. Nevertheless, despite its protective function, pain is one of the clinical symptoms of the disease. Acute pain requires the cause to be determined, emergency to be excluded, and appropriate care to be provided, while in case of chronic pain, it is difficult to eliminate the cause, which is usually already known, and the main goal is to provide an adequate pain relief, which sometimes can be quite difficult (24).

Postsurgical pain in children is one of the main factors determining the child's condition after surgery and contributing to complication development; therefore, pain management in the postoperative period is the

main goal of intensive care. In paediatrics, regional anaesthesia (RA) is one of the most valuable and safest means of perioperative pain management, being an essential part of modern anaesthetic practice (22). Novel RA techniques, especially the anterolateral and the posterolateral trunk blocks, are quite promising today. The benefits of RA in children include: accelerated recovery; reduced opioid use; reduced incidence of postoperative nausea and vomiting; reduced postoperative pain intensity; reduced incidence of respiratory complications (17, 20); reduced healthcare system costs (2, 15). The quadratus lumborum block (QLB) is recommended for surgeries during which both the somatic and visceral components of pain should be affected, including Cesarean section (29), gynaecological surgical procedures such as hysterectomy (6), small bowel resection (5), large bowel resection (30), nephrectomy, colostomy closure, appendectomy (14), gastrectomy, hernia repair (7). Cases of QLB application after bifemoral shunting and cholecystectomy have been described as well (26). The transversalis fascia plane block (TFPB) is a truncal block that targets the L1 nerve branches, namely the ilioinguinal and iliohypogastric nerves, where they emerge from the lateral border of the psoas major muscle, inferior to the 12th rib; the TFPB was first proposed by Hebbard in 2009 (9, 25, 27).

The aim of the study was to assess changes in the serum CD40L level and its potential relationship with pain intensity in children after anterior abdominal wall surgery on the background of general anaesthesia and its combination with various RA techniques.

Materials and methods

The study included 87 (46 boys and 41 girls) children at the age of 7 – 18 years who were treated at the surgical department of a Communal Non-Profit Enterprise “Ivano-Frankivsk Regional Children's Clinical Hospital of Ivano-Frankivsk Regional Council”, Ivano-Frankivsk, Ukraine, and underwent anterior abdominal wall surgery for inguinal hernia, appendicitis using different analgesic techniques during 2020 – 2022. Inclusion criteria were children with inguinal hernia and appendicitis ASA grades I – II at the age of 7 – 18 years, with the mandatory parental consent to involve their child in clinical research. Exclusion criteria included children under 7 years of age; those with ASA grade III or higher, mental disorders, neoplasms, or tumors, acute or inflammatory processes of any aetiology and localization, sepsis, shock; those who previously underwent lower abdominal surgery; those who experienced pain for six months prior to surgery; those who refused to participate in the research; children whose parents refused to give consent and children who gave no consent. All children included in the study were COVID-19 negative at the time of the operation, which was confirmed by a negative antigen, and later by PCR test (18). Patients who tested positive for COVID-19 were isolated and treated according to the pediatric COVID-19 protocol (8, 10, 11).

All children were divided into 3 groups: Group I included 33 children who underwent anterior abdominal wall surgery under general anaesthesia using morphine; Group II comprised 27 children who underwent anterior abdominal wall surgery under general anaesthesia using the TFPB; Group III included 27 children who underwent anterior abdominal wall surgery under general anaesthesia using the TFPB, combined with the QLB-4 via a single injection.

All clinical and laboratory studies were conducted in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". According to the Law, prior to a subject's participation in the study, a written informed consent form was signed by each subject (parents/adult guardians). The manuscript was approved by the Ethics Committee of the Communal Non-Profit Enterprise "Ivano-Frankivsk Regional Children's Clinical Hospital of Ivano-Frankivsk Regional Council", as evidenced by an Excerpt from the Minute of the Committee Meeting No. 2 dated February 24, 2022.

Statistical analysis was carried out on a personal computer using statistical software packages MS Excel, SPSS22 for Windows. The results obtained are presented as $\bar{x} \pm m$. The Shapiro - Wilk test was used to test for a normal distribution. The non-parametric Mann - Whitney U test was applied to compare differences between the indicators (if the outcome was not normally distributed). The relationship between the indicators was determined using Spearman's correlation. In addition, the percentile method was used (median P_5 , P_{10} , P_{25} , P_{50} , P_{75} , P_{90} , P_{95} were determined). Differences were considered statistically significant at $p < 0.05$.

Results

First, changes in the serum CD40L level in children after anterior abdominal wall surgery on the background of general anaesthesia and its combination with various RA techniques were assessed (Tab. 1).

In children receiving general opioid anaesthesia, two hours after surgery, the serum level of CD40L was high; its median was 4.283 pg/ml with the interquartile range (P_{25} - P_{75}) of 4.024-4.583 pg/ml. One day after surgery, the mean serum concentration of CD40L reduced as compared to that observed two hours after surgery; however, there were no statistically significant differences ($U_{\text{Mann-Whitney}} = 52$; $p = 0.563$). At discharge, the mean serum level of CD40L was still high and did not significantly differ from that observed 24 hours after surgery ($U_{\text{Mann-Whitney}} = 52.5$; $p = 0.593$).

In patients receiving general anaesthesia, combined with the TFPB, two hours after surgery, the mean serum concentration of CD40L reduced significantly by 25.3% ($U_{\text{Mann-Whitney}} = 10.0$; $p = 0.002$) as compared to that in patients receiving general anaesthesia alone: the median was 3.135 pg/ml and the interquartile range (P_{25} - P_{75}) was 2.440-3.587 pg/ml. Twenty-four hours after surgery, the mean serum level of CD40L reduced by 15.1% ($U_{\text{Mann-Whitney}} = 26.0$; $p = 0.20$) as compared to

that observed two hours after surgery and by 33.3% ($U_{\text{Mann-Whitney}} = 10.0$; $p = 0.003$) as compared to that in patients receiving general opioid anaesthesia alone. At discharge, the mean serum level of CD40L reduced significantly by 54.4% ($U_{\text{Mann-Whitney}} = 7.0$; $p = 0.003$) as compared to that seen during the previous observation period in this group and by 68.5% ($U_{\text{Mann-Whitney}} = 3.0$; $p = 0.000$) as compared to the corresponding indicator in the group of general anaesthesia.

In children receiving general anaesthesia, combined with single-injection intramuscular TFPB+QLB-4, during all observation periods, the mean serum level of CD40L was 4-7.6 times lower ($U_{\text{Mann-Whitney}} = 0.0$; $p = 0.000$) than corresponding levels in children receiving general anaesthesia, combined with the TFBP. Twenty-four hours after surgery, the mean serum concentration of CD40L reduced significantly by 39.6% ($U_{\text{Mann-Whitney}} = 12.0$; $p = 0.012$) as compared to that observed two hours after surgery. The lowest serum level of CD40L was recorded at discharge: the median was 133 pg/ml, and the interquartile range (P_{25} - P_{75}) was 69.4-188 pg/ml.

Table 1. Changes in the serum level of CD40L in children after anterior abdominal wall surgery using general anaesthesia and its combination with various regional anaesthesia techniques.

Tabuľka 1. Zmeny sérovej koncentrácie CD40L u detí po operácii prednej brušnej steny s použitím celkovej anestézie v kombinácii s rôznymi technikami regionálnej anestézie.

Group	Type of anaesthesia	n	CD40L, pg/ml		
			Observation period		
			2h after surgery	24h after surgery	at discharge
1	General anaesthesia	33	4.191±160	3.984±245	3.847±271
2	General anaesthesia + the TFBP	27	3.130±248*	2.657±292*	1.211±188*§
3	General anaesthesia + the TFBP + the QLB-4	27	758±81.2*#	458±62.3*#§	159±36.7*#§

* - $p < 0.05$ in relation to the corresponding indicator in patients receiving general anaesthesia alone during a particular observation period; # - $p < 0.05$ in relation to the corresponding indicator in patients receiving general anaesthesia, combined with the TFBP, during a particular observation period; § - $p < 0.05$ in relation to the corresponding indicator within the group during the previous observation period.

The results obtained showed that single-injection TFPB+QLB-4 resulted in the lowest mean serum level of CD40L, which was significantly different from those observed with other types of anaesthesia.

Discussion

The relationship between the serum level of CD40L and the level of pain intensity in children after surgery using different types of anaesthesia was assessed as well (Tab. 2). The correlation and percentile analyses provided relevant evidence of CD40 pathway involvement in the development of postsurgical pain in children receiving different types of anaesthesia. Between the serum level of CD40L and the mean score of pain intensity on the visual analogue scale (VAS), a statistically significant and moderate positive correlation was found.

Table 2. Relationship between serum CD40L level and pain intensity level in children after anterior abdominal wall surgery using general anaesthesia and its combination with various regional anaesthesia techniques.

Tabuľka 2. Vzťah medzi sérovou koncentráciou CD40L a intenzitou bolesti u detí po operácii prednej brušnej steny s použitím celkovej anestézie a jej kombinácie s rôznymi technikami regionálnej anestézie.

Indicator	CD40L, pg/ml			Correlation coefficient
	1	2	3	
	0-25 percentile <671 pg/ml n = 29	25-75 percentile 671-3,971 pg/ml n = 29	75-100 percentile >3.971 pg/ml n = 29	
Mean VAS score	3.09±0.17	5.19±0.18	7.27±0.12	$r_s = 0.62$
p	-	$p_{1-2}<0.01$	$P_{2-3}<0.01$ $p_{1-3}<0.001$	$p<0.001$

The subscripts below p indicate the numbers of groups between which the significance of differences was assessed.

The percentile analysis results showed that pain intensity level on the VAS scale was the lowest with low serum levels of CD40L (corresponds to the interquartile range P_0 - P_{25}). Pain intensity was significantly higher with moderate serum concentration of CD40L (corresponds to the P_{25} - P_{75} interquartile range): the mean VAS score was 68% higher than that with low serum CD40L concentrations. A high serum level of CD40L (corresponds to the P_{75} - P_{100} interquartile range) was accompanied by maximum pain intensity – the mean VAS score exceeded the corresponding indicator for moderate serum CD40L concentration by 40% and was 2.4 times higher than that with low serum CD40L levels.

Conclusions

The results of our study provided evidence of CD40L signaling involvement in the development of postsurgical pain in children receiving different types of anaesthesia.

The indicators of CD40L signaling were found to increase in paediatric anterior abdominal wall surgeries.

A combination of conventional anaesthesia and RA techniques resulted in significantly lower serum CD40L levels as compared to the group of general anaesthesia.

There was a close positive correlation between postsurgical pain intensity and CD40L serum levels. Single-injection TFBP+QLB-4 resulted in the lowest serum CD40L levels, an indicative of the lowest intensity of postsurgical pain.*

***Acknowledgment.** We would like to thank the A. Getlik Clinic for Children and Adolescents, Slovak Medical University and University Hospital of Medicine in Bratislava, Slovakia, for administrative support and assistance.

Conflicts of Interest. The authors declare that there is no conflict of interest.

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Do redakcie došlo 20. 11. 2023.

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