ID Design 2012/DOOEL Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2017 Feb 15; 5(1):54-57.
https://doi.org/10.3889/oamjms.2017.024
eISSN: 1857-9655
Clinical Science

Tumour Necrosis Factor-A, Interleukin-1 and Interleukin-6 Serum Levels and Its Correlation with Pain Severity in Chronic Tension-Type Headache Patients: Analysing Effect of Dexketoprofen Administration

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Citation: Rambe AS, Sjahrir H, Machfoed MH. Tumour Necrosis Factor-A, Interleukin-1 and Interleukin-6 Serum Levels and Its Correlation with Pain Severity in Chronic Tension-Type Headache Patients: Analysing Effect of Dexketoprofen Administration. Open Access Maced J Med Sci. 2017 Feb 15; 5(1):54-57. https://doi.org/10.3889/oamjms.2017.024

Keywords: chronic tension; type headache; Dexketoprofen; IL-1; IL-6; TNF-α.

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Received: 23-Dec-2016; **Revised:** 29-Dec-2016; **Accepted:** 26-Jan-2017; **Online first:** 10-Feb-2017

Funding: This research did not receive any financial support.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

AIM: The purpose of this study is to see the effect of Dexketoprofen on TNF-α, IL-1, and IL-6 serum levels in Chronic Tension-Type Headache (CTTH) patients and its correlation with pain severity.

METHOD: The study subjects were recruited consecutively from the study population. Venous blood was taken at baseline to measure serum levels of TNF-α, IL-1, and IL-6 and after ten consecutive days of Dexketoprofen 25 mg once daily.

RESULTS: Twenty three subjects participated in this study, 3 male (13.0%) and 20 female (87%). A significant difference between NRS score at baseline and after treatment (4.86 ± 1.82 vs. 1.96 ± 1.40, p = 0.001) was found. No significant difference found between baseline and after treatment TNF-α (1.48 ± 0.65 pg/dl vs. 1.48 ± 0.63 pg/dl, p = 0.963), IL-1 (0.16 ± 0.80 pg/dl vs. 0.26 ± 0.31 pg/dl, p = 0.168) nor IL-6 serum levels (1.06 ± 0.83 pg/dl vs. 1.04 ± 0.81 pg/dl, p = 0.915). A weak negative (R = -0.266) non significant correlation (p = 0.219) was found between NRS score and TNF-α. A positive weak negative (R = 0.221) non significant correlation (p = 0.311) between NRS score and IL-1. NRS score and IL-6 had a negative very weak (R = -0.019) non significant negative correlation (p = 0.931).

CONCLUSIONS: Dexketoprofen decreased pain intensity significantly (p = 0.001), but had no effect on TNF-α IL-1 nor IL-6 serum levels. NRS score had a weak and non significant negative correlation with TNF-α, a weak and non significant positive correlation with IL-1, and a very weak and non significant negative correlation with IL-6 serum levels.

Introduction

A tension-type headache (TTH) is the most common form of a primary headache. Chronic tension-type headache (CTTH) differs from the episodic forms not only in frequency but also on pathophysiology, lack of effect of most treatment strategies, more medication overuse, more disability, and higher personal and socioeconomic costs [1]. Globally, the percentages of the adult population with an active headache disorder are 46a % headache in general, 11a % migraine, 42% TTH and 3% chronic daily headache [2].

In the past, several studies have measured the levels of cytokines in the blood of headache patients, mostly migraine. Bo *et al.,* studied the level of cytokines in cerebrospinal fluid (CSF) in headache patients and found elevated levels of IL-1, TGF-b1 (*transforming growth factor-b1*), and MCP-1 (*monocyte chemoattractant protein-1*) in episodic tension-type headache (ETTH) and migraine compared to controls, and there were significant differences in MCP-1 between carcinogenic headache and migraine without aura [3]. Kocer found an increasing level of IL-6 in patients with ETTH and CTTH compared to controls. Therefore, they believe that IL-6 is involved in the induction of pain or inflammatory mechanisms in TTH [4]. One study by Backonja also found elevated receptor levels of TNF

in CSF and blood, elevated levels of IL-1β in CSF that was associated with pain intensity, whereas IL-10 was inversely correlated with pain symptoms [5]. Serum levels of IL-1β were significantly elevated in CTTH patients compare to healthy controls, while IL-18 levels were significantly elevated in men with CTTH, in a study by Vedova *et.al* [6].

Dexketoprofen Trometamol, a COX-inhibitor is administered orally with max 0.25-0.75 hours. Dexketoprofen is superior to placebo in relieving moderate to severe pain. Dose-response relationship between 12.5 mg and 25 mg can be seen as a time-effect curve, where the superiority of Dexketoprofen 25 mg is more likely due to the duration of action expansion more than increasing dosage. The medicine is also well tolerated [7].

Prior studies have found a positive relationship between the numbers of cytokines with some types of a headache. Unfortunately, most measurements of cytokine levels were performed in the CSF make it relatively difficult for routine examination in daily practice. The purpose of this study is to measure the serum levels of TNF-α, IL-1, IL-6 in CTTH patients before and after given Dexketoprofen and its correlation with pain severity.

Material and Methods

This research was done at the Adam Malik Hospital and Bukit Barisan Army Hospital Medan, Indonesia from January 2013 - June 2014 and approved by the Ethics Committee for Health Research School of Medicine in University of Sumatera Utara. The subjects were recruited consecutively from the study population. Diagnosis of CTTH was made based on the diagnostic criteria as stated in the ICH-X. NRS score was taken from all subjects at baseline as well as blood for TNF-α, IL-1 and IL-6 serum level measurement. Each subject was given Dexketoprofen 25 mg once daily for ten consecutive days. The day after the last dosage, all subjects were asked to score their pain severity at that time by using NRS. The second blood samples were taken for the second TNF-α, IL-1 and IL-6 serum level measurement. T-paired test with the level of significance $p < 0.5$ was performed to analyse differences between NRS score, TNF-α, IL-1 and IL-6 serum before and after Dexketoprofen administration.

Results

Data from 23 subjects who followed the whole procedure were analysed further. Twenty-three CTTH patients participated in this study, three subjects were men (13.0%), and 20 subjects were women (87%). There was a significant difference ($p = 0.001$) between baseline NRS score (4.86 ± 1.82) with NRS score after Dexketoprofen administration (1.96 ± 1.40). No significant difference ($p = 0.963$) was found between baseline TNF-α (1.48 ± 0.65 pg/dl) with TNF-α level after treatment (1.48 ± 0.63 pg/dl). There is also no significant difference was found between baseline and after 10-day Dexketoprofen administration for IL-1 serum (0.16 ± 0.80 pg/dl vs 0.26 ± 0.31 pg/dl, $p = 0.168$) and IL-6 serum (1.06 ± 0.83 pg/dl vs 1.04 ± 0.81 pg/dl, $p = 0.687$) (Table 1).

Table 1: NRS score, TNF-α, IL-1 and IL-6 serum level before and after Dexketoprofen administration

Variable	Dexketoprofen		*p* *
	Before (n ; x ± SD)	After (n ; x ± SD)	
NRS	23 ; 4,86 ± 1,82	23 ; 1,96 ± 1,40	0,001 **
TNF-α	23 ; 1,48 ± 0,65	23 ; 1,48 ± 0,63	0,963
IL-1	23 ; 0,16 ± 0,80	23 ; 0,26 ± 0,31	0,168
IL-6	23 ; 1,06 ± 0,83	23 ; 1,04 ± 0,81	0,915

After Dexketoprofen administration, the NRS score showed a weak negative and non-significant correlation with the serum level of TNF- α ($R = -0.266$; $p = 0.219$). NRS score has a weak positive non significant correlation with IL-1 serum level ($R = 0.221$; $p = 0.311$), and a very weak negative and non significant correlation with IL-6 ($R = -0.019$; $p = 0.931$) (Table 2).

Table 2: Correlation between NRS score and TNF-α, kadar IL-1 and kadar IL-6 serum level after Dexketoprofen administration

			TNF-α	IL-1	IL-6
NRS after administration	Dexketoprofen	R	-0,266	0,221	- 0,019
		P	0,219	0,311	0,932
		N	23	23	23

Discussion

At baseline, the mean of the NRS score was 4.86 ± 1.82 and became 1.96 ± 1.40 after Dexketoprofen administration. There was a significant decrement of the NRS score with $p = 0.001$. This fact suggests that Dexketoprofen is effective to lower the pain intensity in CTTH patients. Dexketoprofen is an (S)-enantiomer of ketoprofen. Ketoprofen racemic is an effective analgetic and anti-inflammatory agent and consider as a potent inhibitor of prostaglandin synthesis in vitro [7]. Dexketoprofen is a nonsteroidal anti-inflammatory drug which inhibits the cyclo-oxygenase one dan two enzymes (COX-1 dan COX-2) centrally and peripherally [8]. The facts that Dexketoprofen significantly decreased the pain intensity, but has no effect on the serum levels of TNF-α, IL-1 and IL-6 proved that these cytokines play non-significant roles in the pathophysiology of pain in CTTH patients. This study also found inconsistent correlations between NRS and TNF-α, IL-1 and IL-6 serum levels, furthermore, support the possibility of other mechanisms that may be responsible for pain generating process in CTTH patients.

Before Dexketoprofen administration, the mean of TNF-α serum level was 1.48 ± 0.65 pg/dl and became 1.48 ± 0.63 pg/dl after administration. There was a non-significant change of the mean of TNF-α serum level (p = 0.963). This data suggest that TNF-α serum level had no correlation with decreased pain intensity after Dexketoprofen administration in CTTH patients, differs from the previous study. A study by Bo *et.al* in 2008, showed significant differences between the CSF level of IL-1ra, TGF-β1 and MCP-1 in TTH and migraine patients when compared to the control group [3]. The non-significant result of TNF-α in this study is by several previous studies. Tanure *et.al.* found no significant difference in the level of TNF-α, sTNFR1 and sTNFR2 during a migraine attack and headache-free period [9]. In headache patients, the cytokines were only increased slightly if compared to other severe neurological diseases. This increment was considered as a slight response of cytokine toward a headache [10]. A study by Rozen et al. found an increment of TNF-α in CSF of New Daily Persistent Headache (NDPH) and migraine patients. But the increment was not found in serum [11]. TNF-α is the primary pro-inflammatory cytokine for brain infection diseases. In normal condition, this cytokine is produced in a very small quantity. In the state of infection, where there is a strong stimulation by microorganisms, the production will greatly increase so that it can be detected in blood with a quite significant level [12]. The non-significant finding in this study maybe due to the measurement of TNF-α was performed in the serum where more confounding variables found compare to CSF. The very low serum level of TNF-α found in this study was probably indicated that in CTTH patients, the only very small amount of TNF-α produced, in contrast with during brain infection.

There was a contradictory of significance in the result between NRS score and TNF-α serum level, before and after Dexketoprofen administration. With p = 0.001, Dexketoprofen effectively reduced pain intensity. On the other side, p = 0.963 after Dexketoprofen administration, suggest that TNF-α level was not significantly decreased as a result of Dexketoprofen administration. This fact suggests that pain intensity decrement due to Dexketoprofen administration was not through TNF-α decrement mechanism. Regarding pain, there were still many biological mechanisms of Dexketoprofen, which were still not fully understood [13]. Many in vitro studies regarding the effect of TNF-α on CNS has been performed, with still ambiguous conclusions [14]. Before Dexketoprofen administration, the mean level of IL-1 was 0.16 ± 0.80 and it became 0.26 ± 0.31 after administration (p = 0.168). This fact showed that IL-1 serum level did not significantly decrease pain intensity as a result of Dexketoprofen administration in chronic TTH patients. Together, IL-1 and IL-6 causes trigeminal nociceptor sensitization and play an important role in migraine pathogenesis by reducing sensitivity threshold toward other inflammatory stimulus [15]. As strong mediators for fever, pain, and inflammation, IL-1 and TNF-α function via hypothalamic induction [12, 16]. Research by Bo et al found an increment of cytokine IL-1, TGF-β1 and MCP-1 level in ETTH and migraine patients' CSF [3]. The non-significant result on the IL-1 level in this research was by previous studies. In normal condition, the IL-1 production is very small. In infection condition, where there is a strong stimulation by micro organisms, the production will greatly elevate so that it can be detected in blood with a quite significant level [12]. The small quantity of IL-1 in this study was caused by an inflammatory process such as in TTH and not an infectious process of the brain.

There was contradictory of significance in the result between NRS score and IL-1 serum level, before and after Dexketoprofen administration. With p = 0.001, it means that Dexketoprofen effectively reduced pain intensity. On the other side, p = 0.168 after Dexketoprofen administration, suggests that IL-1 level was not significantly different as a result of Dexketoprofen administration. This fact suggests that pain intensity decrement due to Dexketoprofen administration was not through IL-1 decrement mechanism. Regarding pain, there were still many biological mechanisms of Dexketoprofen, which were still not fully understood [13]. The correlation between IL-1 and Dexketoprofen in reducing pain intensity is still unclear.

Before drug administration, the level of IL-6 = 1.06 ± 0.83, and after administration, it became 1.04 ± 0.81 with no significant difference between them (p = 0.915). This fact showed that IL-1 serum level did not significantly decrease pain intensity as a result of Dexketoprofen administration in chronic TTH. Interleukin-6 function as a pro and anti-inflammation, secreted by T-cell and acts as an initial response toward infection and trauma. This substance can penetrate the blood-brain barrier and initiates PGE_2in hypothalamus, thus elevating body temperature. Whenever infection occurs, production of IL-6 will increase [17]. Systemic effect of IL-1 will cause induction of fever, acute phase protein plasma synthesis by the liver, and directly stimulate the production of IL-6, and production of neutrophil and platelet in bone marrow [15]. In migraineurs, it has been suggested that IL-6 level increase during the headache phase. A study by Yan et al. showed that IL-6 strengthen excitability of dura mater afferent fibre so that sensitization which contributed toward a pathophysiology migraine headache occurred [18].

From statistical analysis, there was a non-significant difference of IL-6 level, with p = 0.915, after Dexketoprofen administration. The non-significant result of IL-6 in this study was supported by previous study results. The same as TNF-α and IL-1, IL-6 is very responsive toward infection [17]. Regarding pain in an animal experiment, IL-6 can stimulate trigeminal

ganglion cell to synthesise COX-2 and PGE2, which will release CGRP that causes pain [19]. Bo et al. did not reveal any significant difference in CSF level of several pro-inflammatory cytokines in TTH, migraine, and carcinogenic headache [3]. But, IL-6 pain-related detection in those studies was obtained through LCS, not serum.

There was contradictory of the result between NRS score and IL-6 serum level, before and after Dexketoprofen administration. With p = 0.001, it means that Dexketoprofen effectively reduced pain intensity. On the other side, p = 0.915 after Dexketoprofen administration, suggest that IL-6 level was not significantly different as a result of Dexketoprofen administration. Regarding pain, there were still many biological mechanisms of Dexketoprofen, which were still not fully understood [13]. This fact suggests that pain intensity decrement due to Dexketoprofen administration was not through IL-6 decrement mechanism.

In these subjects, there was statistically significant decrement of pain intensity based on the mean of NRS score (p = 0.001), from 4.86 ± 1.82 (before) to 1.96 ± 1.40 (after). There was a non significant (p = 0.963) change of the mean of TNF-α serum level, from 1.48 ± 0.65 pg/ml (before administration) to 1.48 ± 0.63 pg/ml (after administration). As for IL-1 and IL-6 serum level, there was also non-significant difference between before and after administration (p = 0.168 and p = 0.915 respectively). After Dexketoprofen administration, TNF-α serum level had a weak negative correlation (R = -0.266) and non-significant (p = 0.219) with pain intensity. There was a weak, non-significant positive correlation (R = 0.221; p = 0.311) between pain intensity and IL-1 serum level and a very weak, non-significant correlation (R = -0.019; p = 0.932) between pain intensity and IL-6 serum level.

Acknowledgement

Authors acknowledge the immense help receive from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

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