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 Dextroprofen Administration

Aidy Safrudin Rambe & 1, Hasan Sjahri & 1, Moh Hasan Machfoed & 2

1 The University of North Sumatra, Department of Neurology, Medan, Indonesia; 2 University of Airlangga, Department of Neurology, Surabaya, Indonesia

Abstract

AIM: The purpose of this study is to see the effect of Dextroprofen 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 Dextroprofen 25 mg once daily.

RESULTS: Twenty-three subjects participated in this study, 13 male (13.0%) and 20 female (67%). A significant difference in TNF-α between NRS score at baseline and after treatment (1.49 ± 1.60 pg/dL vs. 1.06 ± 1.40, p = 0.031) was found. No significant differences were found between baseline and after treatment TNF-α (1.49 ± 0.65 pg/dL vs. 1.49 ± 0.63 pg/dL, p = 0.823), 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 ± 0.53 pg/dL vs. 1.04 ± 0.81 pg/dL, p = 0.315). 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: Dextroprofen decreased pain intensity significantly (p = 0.001), but had no effect on TNF-α, IL-1, or 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 46% in men and 21% in women, and 3% of the adult population have 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 certain 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 that IL-6 is involved in the induction of pain or inflammatory mechanisms in TTH [4]. One study by Backenja also found elevated receptor levels of TNF-α.
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 compared 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 Dextketothenprofen 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 as 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 Dextketothenprofen 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 Dextketothenprofen 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 Dextketothenprofen administration.

Results

Data from 23 subjects who followed the whole procedure were analysed further. Twenty-three CTTH patients participated in this study. There were three subjects were men (13.0%), and 20 subjects were women (87%).

Discussion

At baseline, the mean of the NRS score was 4.86 ± 1.82 and became 1.96 ± 1.40 after Dextketothenprofen administration. There was a significant decrement of the NRS score with p = 0.001. This fact suggests that Dextketothenprofen is effective to lower the pain intensity in CTTH patients. Dextketothenprofen is an (S)-enantiomer of ketoprofen. Ketoprofen racemic is an effective analgesic and anti-inflammatory agent and consider as a potent inhibitor of prostaglandin synthesis in vitro [7]. Dextketothenprofen is a nonsteroidal anti-inflammatory drug which inhibits the cycloxygenase one dan two enzymes (COX-1 dan COX-2) centrally and peripherally [8]. The facts that Dextketothenprofen 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 Dextroketoprofen 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 Dextroketoprofen administration in CTTH patients, differs from the previous study. A study by Bo et al. in 2012 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 microorganisms, 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 Dextroketoprofen administration. With p = 0.001, it means that Dextroketoprofen effectively reduced pain intensity. On the other side, p = 0.168 after Dextroketoprofen administration, suggests that IL-1 level was not significantly different as a result of Dextroketoprofen administration. This fact suggests that pain intensity decrement due to Dextroketoprofen administration was not through IL-1 decrement mechanism. Regarding pain, there were still many biological mechanisms of Dextroketoprofen, which were still not fully understood [13]. The correlation between IL-1 and Dextroketoprofen 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 Dextroketoprofen 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 PGE1 hypothalamic, 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].
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 Dextroketoprofen administration. With \( p = 0.001 \), it means that Dextroketoprofen effectively reduced pain intensity. On the other side, \( p = 0.915 \) after Dextroketoprofen administration, suggest that IL-6 level was not significantly different as a result of Dextroketoprofen administration. Regarding pain, there were still many biological mechanisms of Dextroketoprofen, which were still not fully understood [13]. This fact suggests that pain intensity decrement due to Dextroketoprofen 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 change of the mean of TNF-\( \alpha \) serum level, from \( 1.48 \pm 0.65 \) pg/ml (before administration) to \( 1.48 \pm 0.93 \) pg/ml (after administration). For IL-1 and IL-6 serum level, there was also non-significant reference between before and after administration (\( p = 0.168 \) and \( p = 0.915 \) respectively). After Dextroketoprofen administration, TNF-\( \alpha \) 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.

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**References**


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