Open Access Maced J Med Sci **electronic publication ahead of print,**
published on October 14, 2019 as https://doi.org/10.3889/oamjms.2019.426

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.426
eISSN: 1857-9655
Tropical and Infectious Diseases Control and Management

Curcumin's Effect on COX-2 and IL-10 Serum in Preeclampsia's Patient Undergo Sectio Caesarea with Spinal Anesthesia

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Citation: Fadinie W, Lelo A, Wijaya DW, Lumbanraja SN. Curcumin's Effect on COX-2 and IL-10 Serum in Preeclampsia's Patient Undergo Sectio Caesarea with Spinal Anesthesia. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.426

Keywords: Curcumin; Cyclooxygenase 2 (COX-2); Interleukin-10 (IL-10); Preeclampsia; Spinal Anesthesia

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Received: 14-Aug-2019; **Revised:** 15-Sep-2019; **Accepted:** 16-Sep-2019; **Online first:** 14-Oct-2019

Funding: This research did not receive any financial support

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

Abstract

BACKGROUND: Curcumin is a major component in curcuminoid which acts as an anti-inflammatory agent. Curcumin affects several biological markers that are thought to play a role in the pathogenesis of preeclampsia such as IL-10 and COX-2, resulting in an improvement in pregnant women with preeclampsia.

AIM: To see the effect of perioperative curcumin administration on IL-10 and COX-2 in preeclamptic patients undergoing caesarean section under spinal anaesthesia.

METHODS: This study was a double-blind, randomised clinical trial conducted at Pirngadi Hospital, USU Hospital and Sundari General Hospital Medan as a hospital network of Faculty of Medicine, North Sumatra University. Group 1 received a drug containing curcumin (as a treatment), and another group received a placebo (as a control).

RESULTS: There were no significant differences in the median values of COX-2 and IL-10 before and after treatment and also the p-values were greater than 0.05 in both groups (control and treatment).

CONCLUSION: There is no significant difference between the use of curcumin on serum COX-2 and IL-10 levels.

Introduction

Preeclampsia is a disorder in pregnant women with a gestational age of 20 weeks or more which characterised by hypertension and proteinuria that occurs in 5-10% of pregnancies. Preeclampsia also is known by a disorder of extensive endothelial function, starting with placental cytotrophoblast invasion, which can lead to clinical hypertension [1].

In pregnancy, there is a normal change in blood pressure due to hemodynamic changes to allow the exchange of blood and nutrients to the fetus. This circulation change usually occurs in the first trimester of pregnancy, during trophoblast implantation. The vascularisation changes of the decidua make the capacity of blood vessels that are initially high resistance with low capacity to be low resistance with high capacity, and this change will disrupt oxygen supply to the placenta. Increasing gestational age, the fetus will need a higher oxygen supply, but because vasoconstriction that occurs in the fetal blood vessels causes compensation to increase maternal blood pressure [2].

Curcumin which is the main component in curcuminoid theoretically acts as an anti-inflammatory agent by inhibiting NF-κβ activation, which is an important regulator of COX-2 expression [2]. Curcumin has been studied as a therapeutic agent for various types of diseases, the effect of curcumin as antiangiogenic, antioxidant and anti-inflammatory affects several biological markers that are thought to

play a role in the pathogenesis of preeclampsia such as IL-10 and COX-2 so that there is an improvement in women with preeclampsia.

This study was designed to prove that the administration of curcumin can change IL-10 and COX-2 levels and perioperative VAS in preeclamptic patients undergoing cesarean section under spinal anaesthesia.

Material and Methods

This is an experimental double-blind study with the type of pre and post-test control group design. Patients who diagnosed with preeclampsia and met the inclusion criteria, then divided into 2 groups which received drugs containing curcumin (as a treatment) and other group received placebo (as a control). The study was done at H Adam Malik Hospital, Medan, USU Hospital, RSUD dr. Pirngadi Medan, Hospital Putri Hijau Medan and Sundari General Hospital Medan, as a network Hospital for Medical Faculty of USU.

Pregnant preeclampsia women, with age range from 19-40 years, single pregnancy with a term of gestational age and planned for caesarean section with subarachnoid block regional anaesthesia techniques were included to inclusion criteria. Meanwhile, samples who had a systemic infection, chronic diseases (kidney disease & hypertension, diabetes mellitus) were the exclusion criteria for this study. Massive bleeding, patients who needed a hysterectomy, patients who had cardiac arrest and breathing problem during operation and prolong operation time were excluded from the study.

Fifty pregnant women were included in this study and had been informed about the study divided into two groups, one group received curcumin as a treatment group, and the other group received placebo as a control group. Three samples were excluded from this study because after blood samples were taken, the result was unreadable.

All samples who diagnosed with preeclampsia was being informed about the study after informed consent accepted blood were taken to examine all the biomarkers (T0), 90 minutes (T1) after the drugs given, second blood samples were taken for the second examination. Then sectio caesarean operation was done under spinal anaesthesia. 12 hours (T2) after the drugs are given another blood samples were taken to examine the biomarkers. All samples received Magnesium Sulphate based on preeclampsia's guidelines therapy.

Results

In this study, 47 samples were reported and divided into 2 groups, treatment groups (23 samples) and control groups (24 samples). The difference in serum COX-2 levels after being given curcumin is presented in Table 1.

Table 1: Differences in serum COX-2 levels after being given curcumin

Biomarker	Curcumin (-) (n=24)	Curcumin (+) (n=23)	P Value [a)]
COX-2 (T0)	54,95 (15,88 - 300,2)	55,71 (15,88 - 1074,92)	0,285
COX-2 (T1)	55,30 (10,94 - 91,88)	59,40 (33,34 - 489,86)	0,120
COX-2 (T2)	65,14 (23,84 - 91,06)	62,51 (16,4 - 504,96)	0,250
P Value [b)]	0,325	0,438	

Based on Table 1, comparison of COX-2 results in both groups at T0, T1 and T2 showed no significant differences indicated by the median values in the two groups that were not too far different and the p-values indicating values greater than 0.05. That is, from T0, T1 to T2 in both groups (control and treatment) no significant COX-2 levels were found.

Based on the value of COX-2 changes from T0 to T2 in each group indicated by the p-value in the Friedman test. The Friedman test results in the control group produced a p-value of 0.325, which was greater than 0.05, indicating that in the control group, there was no significant change in COX-2 levels from T0 to T2. Similarly, in the treatment group, a p-value of 0.438 which was greater than 0.05 showed that in the control group, there was no significant change in COX-2 levels from T0 to T2 (Figure 1).

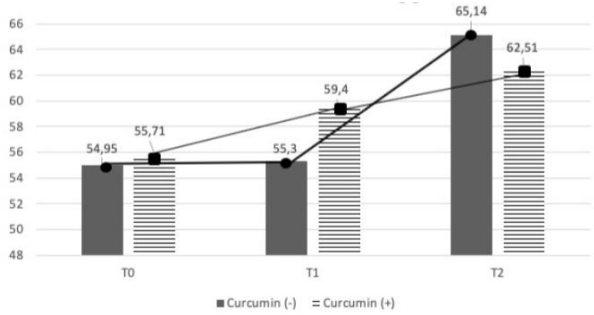

Figure 1: Differences in serum COX-2 levels after being given curcumin

The changes in serum IL-10 levels presented in Table 2, comparison of IL-10 results in both groups at T0, T1 and T2 showed no significant differences indicated by the median values in the two groups that were not too far different and the p-values indicating values greater than 0.05. That is, from T0, T1 to T2 in both groups (control and treatment) there was no significant IL-10 level found.

Table 2: Differences in serum IL-10 levels after being given curcumin

Biomarker	Curcumin (-) (n=24)	Curcumin (+) (n=23)	P Value [a)]
IL-10 (T0)	285,26 (8,32 - 636,4)	287,79 (6,37 - 6950,27)	0,158
IL-10 (T1)	309,8 (131,59 - 371,42)	289,63 (0,10 - 5759,2)	0,201
IL-10 (T2)	289,39 (9,70 - 412,12)	287,72 (1,53 - 6468,53)	0,170
P Value [b)]	0,582	0,296	

Based on the value of IL-10 changes from T0 to T2 in each group indicated by the p-value in the Friedman test. The Friedman test results in the control group produced a p-value of 0.582, which was greater than 0.05, indicating that in the control group, there was no significant change in IL-10 levels from T0 to T2. Similarly, in the treatment group, a p-value of 0.296 which was greater than 0.05 showed that in the control group, there was no significant change in IL-10 levels from T0 to T2 (Figure 2).

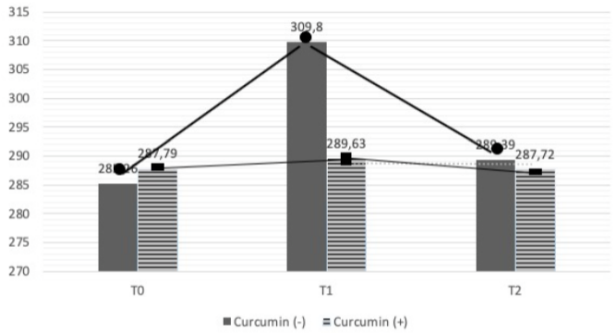

Figure 2: Differences in serum IL-10 levels after being given curcumin

Differences time by time can be seen in Table 3. There were no significant differences in IL-10 p-values (T0-T1 = 0.051, T0-T2 = 0.476 and T1-T2 = 0.317) and in COX-2 (T0-T1 = 0.437, T0-T2 = 0.890 and T1-T2 = 0.191) both in control and treatment groups.

Table 3: Differences in serum IL – 10 and COX-2 levels between observations

Biomarker	Curcumin - (n=24)	Curcumin + (n=23)	P Value
COX-2 T0-T1	-1,38 (-23,87 - 252,49)	-2,87 (-34,54 - 862,96)	0,437
COX-2 T0-T2	-3,83 (-49,67 - 233,45)	-5,36 (-222,48 - 1003,17)	0,890
COX-2 T1-T2	-11,86 (-48,68 - 32,35)	-1,00 (-232,78 - 140,21)	0,191
IL-10 T0-T1	-20,58 (-261,24 - 290,4)	38,34 (-299,42 - 1191,07)	0,051
IL-10 T0-T2	-10,59 (-252,86 - 273,72)	-1,25 (-623,07 - 481,74)	0,476
IL-10 T1-T2	-0,83 (-97,69 - 230,91)	-6,76 (-709,33 - 132,86)	0,317

Discussion

To our knowledge, our research was the first to assess the effect of curcumin in preeclampsia patients. So, the dosage that given was only once daily and only 100 mg of curcumin, although many studies used higher dosage in cancer or neurodegenerative patients.

IL-10 was first reported by Mosmann et al. as Cytokine Synthesis Inhibitory Factor (CSIF) as a protein with the ability to inhibit the activity of Th-1 type cells. CSIF is considered as the main factor that defines the difference between Th-1 and Th-2 type T cells because CSIF cuts T-cell activation. Although initially defined as Th-2 cell products, these cytokines have now been shown to be produced by various types of cells, including immune and non-immune cells. The report also shows that one way of regulating IL-10 is through a feedback loop that inhibits excessive inflammation [3].

IL-10 in humans is a homodimeric protein that is sensitive to monomeric acid with a molecular weight of 18.5 kDa which is encoded on chromosome 1 in mice and humans. IL-10 mice and human IL-10 are sufficiently conserved in their amino acid sequences to share 73% homology and are especially different in human N-glycosylation sites with IL-10 [4].

The serum and amount of placental IL-10 have been reported to increase in normal pregnancies. Sowmya et al., [5], in their study mentioned that variations in IL-10 production are largely genetically determined, which is mainly related to genetic variation in the study area that linked to the level of transcription. A study by Benian et al., [6], in the Istanbul population, have shown levels of IL-10 in plasma and IL-10 in the placenta. In contrast, Madazli et al., [7], reported an increase in IL-10 levels in maternal plasma of preeclamptic patients compared with normotensive women in the Istanbul population. Mansouri et al., [8], conducted a study on serum samples of preeclampsia patients and control subjects and revealed no significant changes in the examination. On the other hand, Makris et al., [9], showed that IL-10 promoter genotypes might not play an important role in circulating IL-10 levels but showed effects on IL-10 placental levels in the study population. This result suggests that IL-10 plays an important role [5].

There is increasing evidence that inflammation with COX-2 expression plays a key role in preeclampsia, so increasing the expression of neutrophils from COX-2 is an important finding regarding the pathophysiology of preeclampsia. Increased COX-2 expression seems to be widespread. COX-2 is increased in the placenta of women with preeclampsia where the expression is associated with an increase in thromboxane production. The placenta from preeclamptic women produces more thromboxane and less prostacyclin than the placenta obtained from normal pregnant women. Thromboxane is a strong vasoconstrictor, whereas prostacyclin is a strong vasodilator, so this imbalance contributes to reduced uteroplacental blood flow in preeclampsia [10].

Curcumin modulates the inflammatory response by reducing the activity of the cyclooxygenase-2 (COX-2) enzyme, lipoxygenase, and inducible nitric oxide synthase (iNOS); inhibits the production of inflammatory cytokines tumour necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP) and protein inhibitory migration also decreases mitogen-regulation activated and Janus kinases. (Julie, 2009). Curcumin is thought to be able to directly act on oxygenation of arachidonic acid or nitrogen-reactive species due to its antioxidant ability. Curcumin can modulate COX-2 via iNOS [11]. Inhibition of COX-2 and iNOS results from suppression of curcumin in NF-κ activation [12].

COX-2 expression regulation occurs not only at the transcriptional level but also at the post-transcriptional level. The main function of COX-2 is to mediate the conversion of arachidonic acid into prostaglandin H2, which is then converted to various PGs with various syntheses. The Study reported that COX-2 provides action on cell function, including modulation of cell proliferation and cell migration. Other researchers have reported the role of COX-2 in angiogenesis, seen by using a modified vascular endothelial growth factor (VEGF) as an endpoint. However, in the human placenta, the results are inconsistent, with several studies showing placental COX-2 levels not to differ between normal pregnancies and preeclamptic pregnancies. Others found that COX-2 levels in preeclamptic women were reduced as measured by immunoblotting, and this effect has been linked to oxidative stress [13].

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