Original Article

CURCUMIN AND ITS EFFECT ON PREECLAMPSIA: AS ANTI-INFLAMMATORY, ANALGESIC, AND ANTICOAGULANT

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ABSTRACT

Objective: Based on the Indonesia Health Profile In 2014, almost 30% of maternal deaths at Indonesia in 2010 were caused by hypertension in pregnancy, which one of them was preeclampsia. Many theories said to be the risk factor, such as acute body inflammation. Its clinical symptoms are hypertension, upper abdominal pain, and haemorrhage. Nowadays, many studies have been developed to predict the onset of preeclampsia, one of which is COX-2. This study was the first one to examine the benefits of curcumin in preeclamptic patients around the world.

This study aims to discover whether curcumin affects the level of COX-2, VAS, and anticoagulant factors in preeclamptic patients.

Methods: This is true experimental research with a double-blind randomized design. 50 samples were collected within a period of 7 mo and were divided into 2 groups: Case and Control Group. A total of 3 blood tests were conducted: prior, 90 min, and 12 h after case/treatment.

Results: 4 samples were eliminated during preparation. The total number of samples was 46; 23 in Control Group and 23 in Case Group. In this study, we found clinical changes in the level of COX-2, VAS and anticoagulant factors in patients given 100 mg of curcumin compared to those who were not. In addition, we also found a correlation between clotting time and bleeding time at T2 where both time factors became shorter.

Conclusion: There was a statistically significant decrease in COX-2 level in the Case Group, which led to decreased value of VAS, shorter clotting time and lower thrombocyte count; and, there was a significant correlation found between clotting time and bleeding time at T2 in the preeclamptic patients.

Keywords: Preeclampsia, COX-2, Curcumin, VAS, Anticoagulant factor

INTRODUCTION

The ethiology of preeclampsia is still largely unknown. However, several theories postulate that is caused by acute inflammation and angiogenesis imbalance. Endothelial dysfunction has recently also been associated as a factor that triggers clinical symptoms of preeclampsia; and some factors that affect endothelial dysfunction are reduced placental perfusion and placental ischemia, thereby causing an imbalance in angiogenesis factor, oxidative stress and over-activated inflammatory process [1]. Therefore, preeclampsia can be defined as a complex maternity (pregnancy-specific) syndrome caused by placental hypoperfusion and extensive endothelial dysfunction due to the release/activation of inflammatory cytokines and angiogenic proteins [2]. Based on the study by Saraswati *et al.*, the rate of maternal mortality in Indonesia ranges between 3–10%, in which 28% is caused by severe haemorrhage, 24% preeclampsia, 11% infection, 8% puerperium complication, 5% prolonged parturition/labor and 5% abortion [3].

Curcumin (*1.7-bis (4-hydroxy-3-methoxyphenyl)-1.6-heptadiene-3.5-dione)* also known as *diferuloylmethane*, is a polyphenol naturally found in *rhyzome Curcuma Longa* (turmeric). Curcumin is widely used in food, beverage, health supplement and even cosmetics industry. *Curcuminoids* has been approved by US Food and Drug Administration (USFDA) as *"Generally Recognized as Safe"* (GRAS) [4]. Curcumin has anti-inflammatory effects on several biomarkers presumed to influence the pathogenesis of preeclampsia e. g. COX-2 level that contributes to the recovery of preeclamptic patients. It is hoped that curcumin given as a supplement could help lower COX-2 levels and reduce the morbidity rate of postpartum preeclampsia.

MATERIALS AND METHODS

Study design

This research is a true experimental double-blind study with a pretest-posttest control group design. The samples are patients clinically diagnosed with preeclampsia who fulfill the inclusion criteria. The samples are divided into 2 groups: the first group received the case medicine (treatment) containing 100 mg curcumin (known as the Case Group), and the second group received the placebo (known as the Control Group). The samples were collected consecutively with randomized case.

Time and location of research

The experiment was conducted at three different hospitals: Hospital of Universitas Sumatra Utara (USU), dr. Pirngadi General Hospital and Sundari Hospital in Medan, within the time frame necessary to fulfill the required number of samples since obtaining the approval of the Ethics Committee in October 2019.

Population and research samples

This is the first study conducted on the effects of curcumin administration to the sample population of pregnant women with preeclampsia who met the inclusion criteria (pregnant preeclamptic female, age 19-40 y, single live pregnancy carried full term, and planned C-section using spinal anesthesis technique) and did not present any of the exclusion criteria (existing systemic and chronic infection), and agreed to participate in the experiment by filling and signing the informed consent papers.

Research procedures

After being reviewed and approved by the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, the patients who met the inclusion criteria submitted their personal data to be used as a research subject and subsequently signed the informed consent. The subjects then randomly selected and grouped into 2 categories i.e. the Case Group who received 100 mg curcumin capsules and the Control Group who received placebo capsules. The first haemodynamic examination, VAS measurement and blood test to

check the level of COX-2 and anti-coagulant factors (clotting time, bleeding time, and thrombocyte count) were conducted prior to the case treatment (T0). As soon as the first examination was completed, volunteers immediately gave the 100 mg curcumin capsules to the Case Group and the placebo capsules to the Control Group, so that neither the researchers nor the laboratory staff knew which capsules were given. The second haemodynamic examination, VAS measurement and blood test to evaluate COX-2 and anti-coagulant factors were conducted 90 min after the case treatment (T1). Next, both groups went through the C-section procedure using a subarachnoid block anesthesia technique. 12 h after the case treatment (T2), the third hemodynamic examination, VAS measurement and blood test to check the level of COX-2 and anti-coagulant factors were administered. Finally, researchers collected all the data and lab results to be processed and analized by using computer software.

Ethical statement

The individuals involved in this project hereby declare that this research has been approved by the Committee of Research and Ethics of the Faculty of Medicine, Universitas Sumatera Utara, Indonesia.

Analysis of statistics

This study utilized several different statistics tests. In the beginning, the Saphiro-Wilk test was used to examine the characteristics of the samples. Secondly, to compare the Case Group and Control Group in terms of the relationship between dependent variables i.e. anti-coagulant factors (clotting time, bleeding time, and thrombocyte), VAS and COX-2 at T0, T1 and T2, the Mann Whitney test was employed. Thirdly, to compare and analyze the relationship between dependent variables i.e. anti-coagulant factors, VAS and COX-2 at T0, T1 and T2, the researchers used the Friedman test. Finally, Spearman test was used to compare the clotting time and bleeding time at T0, T1 and T2, in order to find the possible correlation.

RESULTS

Characteristics of samples

Table 1 shows, in terms of age, the highest frequency of sample is found in the age group 26–35 with a total of 17 samples in Control Group (36.95%) and 13 samples in Case Group (28.26%). The average age of samples in Control Group is 30.56 while the average age in Case Group is 32.3. In other words, the total number of samples in Control Group is 23 whose age ranges from 21–42 y and an average value is 30.56 (95% CI = 0.145); and, the sample total in Case Group is 23 whose age ranges from 24–41 and the average value is 32.3 (95% CI = 0.220).

If we look at the samples' ethnicity, they are predominantly Javanese in both Control Group (11 samples, 23.92%) and Case Group (13 samples, 28.27%). In addition, the data results in relation to ethnicity from Control and Case Group are statistically homogenous (p=0.991).

Table 1: Characteristics of samples

		Control group		Case group		Total		P-value*
		N	%	N	%	N	%	
Age	17–25 y	2	4.35	4	8.70	10	13.05	
	26–35 y	17	36.95	13	28.26	31	65.21	0.298
	36–45 y	4	8.70	6	13.04	6	21.74	
	Total	23	50.00	23	50.00	47	100.00	
Ethnicity	Bataknese	7	15.21	7	15.21	15	30.44	
	Javanese	11	23.92	13	28.27	24	52.17	0.991
	Mandailingese	2	4.35	2	4.35	4	8.70	
	Malay	2	4.35	1	2.17	3	6.52	
	Padangnese	1	2.17	0	0.00	1	2.17	
	Total	23	50.00	23	50.00	47	100.00	

Note: p-value determined by Chi-Square test, homogenous characteristics if p>0.05

Anti-coagulant factors (Clotting time, bleeding time and thrombocyte)

Clotting time

Table 2: Comparison of clotting time in control and case group, and changes from T0 to T2

Biomarker		Control group (n=23)	Case group (n=23)	P-value[a)]
Clotting time (T0) (seconds)	Mean ± SD	414.78±41.11	435.65±52.64	0.278
Clotting time (T1) (seconds)	Mean ± SD	418.7±67.98	425.22±69.86	0.767
Clotting time (T2) (seconds)	Mean ± SD	420±36.18	426.52±63.29	0.235
P-value [b)]		0.336	0.829	

Note: p-value determined by a) Mann Whitney test, b) Friedman test.

T0=pre-treatment; T1=90 min post-treatment; T2=12 h post-treatment

The data in table 2 reveals that simultaneously the change in clotting time found in Control Group from T0 to T1 to T2 is not significant (p=0.336). Similarly, Clotting Time in Case Group from T0 to T1 to T2 simultaneously shows statistically insignificant changes (p-value=0.829).

Bleeding time

Table 3: Comparison of bleeding time in control and case group, and changes from T0 to T2

Biomarker		Control group (n=23)	Case group (n=23)	P-value[a)]
Bleeding time (T0) (seconds)	mean±SD	187.83±32.88	177.39±28.48	0.319
Bleeding time (T1) (seconds)	mean±SD	195.65±36.03	182.61±36.08	0.282
Bleeding time (T2) (seconds)	mean±SD	190.43±28.04	187.83±27.46	0.652
P-value[b)]		0.383	0.494	

Note: p-value determined by a)Mann Whitney test, b) Friedman test, T0=pre-treatment; T1=90 min post-treatment; T2=12 h post-treatment, It can be seen from table 3 that simultaneously the Bleeding Time change

from T0 to T1 to T2 in Control Group is not considered significant with p-value=0.383. In Case Group, the Bleeding Time change from T0 to T1 to T2 is likewise not considered significant with p-value=0.494.

Thrombocyte

Table 4: Comparison of thrombocyte in control and case group, and changes from T0 to T2

Biomarker		Control group (n=23)	Case group (n=23)	P-value[a]
Thrombocyte (T0) (/μl)	mean±SD	297608.7±82095.7	304652.17±68046.51	0.800
Thrombocyte (T1) (/μl)	mean±SD	297304.35±71867.58	304000±64418.38	0.660
Thrombocyte (T2) (/μl)	mean±SD	281217.39±70049.95	271521.74±76080.62	0.709
P-value[b]		0.015*	0.104	

Note: p-value determined by a) Mann Whitney test, b) Friedman test, where the difference/change considered *significant if p<0.05, T0=pre-treatment; T1=90 min post-treatment; T2=12 h post-treatment, From table 4 it is clear that simultaneously the

Thrombocyte change in Control Group from T0 to T1 to T2 is considered significant with p=0.015. On the other hand, the Thrombocyte in Case Group from T0 to T1 to T2 simultaneously shows insignificant changes (p=0.104).

Visual analog scale (VAS)

Table 5: Comparison of VAS in control and case group, and changes from T0 to T2

Bio-marker		Control group (n=23)	Case group (n=23)	P-value[a]
VAS (T0) (cm)	mean±SD	2.22±1.48	1.65±0.78	0.320
VAS (T1) (cm)	mean±SD	1.87±1.14	1.57±0.66	0.553
VAS (T2) (cm)	mean±SD	1.83±1.03	1.91±1.24	0.981
P-value[b]		0.248	0.711	

Note: p-value determined by a) Mann Whitney test, b) Friedman test., T0=pre-treatment; T1=90 min post-treatment; T2=12 h post-treatment. Table 5 shows simultaneously the changes in VAS found

in Control Group from T0 to T1 to T2 are not considered significant with p-value 0.248. Similar results can also be found in VAS in Case Group from T0 to T1 to T2 (p-value=0.711).

Cyclooxygenase-2 serum (COX-2)

Table 6: Comparison of COX-2 in control and case group, and changes from T0 to T2.

Biomarker		Control group (n=23)	Case group (n=23)	P-value[a]
COX-2 (T0) (U/l)	mean±SD	90.96±101.09	93.75±214.58	0.089
COX-2 (T1) (U/l)	mean±SD	81.60±90.59	57.89±37.01	0.057
COX-2 (T2) (U/l)	mean±SD	98.30±101.70	60.01±18.25	0.001**
P-value[b]		0.309	0.593	

Note: p-value determined by a) Mann Whitney test, b) Friedman test, where the difference/change considered ** extremely significant if p<0.01, T0=pre-treatment; T1=90 min post-treatment; T2=12 h post-treatment. Table 6 reveals simultaneously that neither the COX-2 change in Control Group nor that in Case Group, from T0 to T1 to T2, is regarded as

statistically significant with p-value 0.309 and 0.593 respectively. When we compare COX-2 in Control Group and COX-2 in Case Group 12 h after treatment (T2), we can see the average value of COX-2 in Control Group is 98.30±101.70 while that in Case Group is 60.01±18.25 with p-value=0.001**. This shows that there is an extremely significant relationship between the two groups at T2.

The correlation between clotting time and bleeding time at T2

Table 7: Correlation between clotting time and bleeding time at T2

	Bleeding time
Clotting time	rs = 0.481*
P-value	0.020

Note: *Spearman rank correlation coefficient, Table 7 presents a statistically significant and strong correlation (p-value=0.020 and rs=0.481) between Clotting Time and Bleeding Time at T2, where both factors show a reduction in time.

DISCUSSION

Characteristics of subjects

In table 1 the highest number of samples in both Control and Case Group is in the age category of 26–35 y old. It corresponds with a previous study reported that averagely preeclampsia most frequently occurred in the age group of 26–30.

The statistics test used to evaluate and compare the subject's characteristics of Control Group and those of Case Group is the *Chi*

Square Analysis, and the data results are found to be homogenous with p-value≥0.005.

Anti-coagulant factors (*Clotting Time, Bleeding Time and Thrombocyte Serum*)

Thrombocyte aggregation plays an important role in the process of thrombosis and haemostasis. Thrombosis is an abnormal blood clotting process in which thrombus (blood clot) is formed inside a blood vessel. There are 3 key factors contribute to the development

of thrombosis: endothelial injury, stasis (abnormal blood circulation) and hypercoagulability.

Increased thrombocyte aggregation in a pregnant female with preeclampsia will lead to a state of *Relative Hypercoagulation* as opposed to a female with normal pregnancy. Thrombocyte degranulation may cause thrombocyte function less effective, and the resulting aggregation reduces the thrombocyte count. Thrombocytopenia in preeclamptic patients can trigger the onset of *Disseminated Intravascular Coagulation* syndrome (DIC) causing a higher frequency of post-partum bleeding occurring in preeclamptic patients compared to normal pregnancy. This finding is supported by previous studies which state that pregnancies with preeclampsia carry averagely lower thrombocyte count as opposed to normal pregnancies; this data is significant statistically with p-value<0.05. The studies found that of 31,560 patients with preeclampsia, 2,347 (7.4%) experienced post-partum haemorrhage; whereas of 1,426,016 those with normal pregnancy, only 60,517 (4.2%) had the condition [9, 10].

Curcumin is a common spice typically used in cooking in Indonesia. It is also considered as a natural herbal remedy due to its beneficial properties. Curcumin anti-platelet activity occurs by inhibiting the activity of COX. The aggregation mediated by *Platelet Activating Factor* (PAF) and *Arachidonic Acid* (AA) work directly or indirectly in the production of TXA. TXA then interacts with its receptors inside the thrombocyte, thus disrupting its aggregating response [11].

A further study had reported that increased *lipoxygenase* (LOX) derivatives were found in patients treated with curcumin. This condition could be due to AA redirection to LOX pathway and/or enzyme potentiation. AA is a fatty acid found in the membrane of the body's cells and metabolized by *cyclooxygenase* (COX) resulting in the synthesization of prostaglandins (PG) *endoperoxide* intermediate such as PGH2. Inside the thrombocyte, *endoperoxides* are then metabolized into thromboxane A2 and PG. Therefore, curcumin's anti-platelet activity may have effects on *cyclooxygenase* (COX) pathway in the thrombocyte's membrane/receptor.

If we look at the mean value, it is apparent that there is a statistically significant decrease in Clotting Time in the Case Group. It can be deduced that curcumin can clinically reduce the blood's Clotting Time. Shorter clotting time is a positive result, meaning the blood-thinning effect of curcumin on thrombocyte does not influence clotting time.

Upon evaluating the mean value of Bleeding Time in both groups, they show no changes and have equal value at all three points of examination (T0-T2) and was also still within the normal range. The constant Bleeding Time may be caused by shorter Clotting Time, as discussed above, which is favorable as it implies the anti-coagulant of curcumin does not affect the Bleeding Time.

This experiment discovered that both Control and Case Group's thrombocyte count decreased from T0 to T2. In addition, the mean value of thrombocyte count in the two groups also showed a clinically significant decline from T0 to T2; albeit the decrease in the Case Group (11.92%) was greater than that in the Control Group (8.37%). Despite a decrease in platelets at this study, thrombocyte count was still within the normal range. This finding suggests that curcumin is able to reduce thrombocyte count clinically, which agrees with a previous study, proving that curcumin does have a blood-thinning effect.

In this study, the minimum level of thrombocyte count found clinically did not reach the level associated with acute/lethal condition of thrombocytopenia. The lowest count (131,000/μl) came from a single sample in the Case Group 12 h after the curcumin treatment (T2). The same sample presented a thrombocyte count of 267,000/μl before treatment, which rose to 275,000/μl 90 min after treatment, and dramatically dropped to 131,000/μl 12 h after. Thus, based on all of the post-treatment results in the Case Group, it can be concluded that even though curcumin has blood-thinning property, it does not lead to acute thrombocytopenia.

As previously stated, curcumin is ubiquitous in Indonesia. It is found in traditional herbal medicine (jamu), phytopharmaceuticals, and even in cooking as spice/seasoning. The existence of an anticoagulant effect in

curcumin consequently means that an anesthesist needs to exercise extra caution when performing spinal anesthesis technique in a C-section. However, this experiment has proven that the effect of curcumin treatment is insignificant to thrombocyte serum level as demonstrated by the constant/unchanged Bleeding Time and the minor reduction in Clotting Time, which are favorable findings for the preeclamptic patients. In short, curcumin does not affect the blood-thinning process and, therefore, is not a contraindication of spinal anesthesia.

Value of VAS

In addition to its hepatoprotector activity, curcumin is also known to have an analgesic effect. Curcumin analgesic activity is associated with its potency as an inhibitor to arachidonic acid metabolism pathway. One of the key factors in the arachidonic acid pathway is the cyclooxygenase enzyme (COX), whereby inhibition in COX-2 is known to affect pain.

Similar to *Nonsteroidal Anti-inflammatory Drugs* (NSAID), curcumin works through a single or a combination of multiple mechanisms involving inhibitions of arachidonic acid, COX, LOX, prostaglandin synthesis, inflammatory cytokines and TNF [14].

NSAID relieves pain by lowering the production of E2 prostaglandin mediated by cyclooxygenase, which is the enzyme presumed to be the primary inflammatory prostaglandin that activates and controls the sensitivity of perpipheral nociceptor responsible for pain sensation. Prostaglandin also plays a role in spinal nociceptor, which further supports the mechanism of NSAID spinal analgesis [15].

Curcumin is capable of increasing PPAR-ɣ, which protects the body from tissue damage such as ischemia caused by bleeding or endotoxemia, as well as reducing inflammatory reaction resulting in weaker pain stimuli [16]. The relationship between curcumin and COX-2 also influences neuropathic pain experienced by patients, whereby curcumin decreases the level of COX-2 serum as well as relieving the pain, and thus decreases VAS in the patients.

The level of VAS in the Case Group was found to be lower; evidence that curcumin does have an analgesic effect via COX-2 inhibition. However, from a statistics point of view, there was no significant difference between the average results of VAS either before or after treatment found in Control and Case Group. This may be the result of $MgSO_4$ regiment in the administration of preeclampsia cases i.e. both groups received MgSO4 regiment once the diagnosis of preeclampsia was established. This drugs regiment is meant to prevent and lower the risk of eclampsia, in addition to reducing the maternal and perinatal morbidity and mortality rate.

The exact mechanism of magnesium sulphate is not yet fully understood. One of its mechanisms known is that it causes vasodilation via relaxation of smooth muscle walls within blood vessels including the peripheral and uterus vessels; thus, besides being an anticonvulsant, magnesium sulphate also works as anti-hypertension and tocolytic drugs. The effect of smooth muscle relaxation inside the uterus can possibly lessen the pain from contraction prior to and/or after labor; less contraction leads to less pain and causes low VAS in perioperative patients.

A research supported the above hypothesis with its finding that patients treated with intravenous MgSO4 showed a lower level of VAS compared to those who did not receive intravenous MgSO4. Shah (2018) claimed that there was a total reduction of additional analgesic and a lower VAS in the group who received intravenous MgSO4 24 h post-surgery. Kahraman (2014) further added that a regiment of 65 mg/kg Body Weight of MgSO4 given intravenously in hysteroctomy surgical procedure using spinal anesthesis technique could prolong the anesthesia's duration of spinal sensory blockade and reduce VAS with no complications [18-20].

Another type of medicine which can help alleviate pain is Bupivacaine. Bupivacaine is known to reduce the level of *Nuclear FaClotting Timeor-Kappa-B* (NF-κB), which means bupivacaine can act as an inhibitor to NF-κB activation in the *dorsal horn* of the lumbar spinal cord. This consequently triggers the COX-2 level to decline, and lessens the pain response [17].

Cyclooxygenase-2 serum (COX-2)

More and more evidence supports the hypothesis that inflammation and COX-2 expression hold a key role in preeclampsia cases. Neutrofil expression of COX-2 is an important finding related to the pathophisiology of preeclampsia. COX-2 in the placenta of a pregnant female with preeclampsia is found to be increased; and its expression contributes to increased thromboxane production. The placenta obtained from preeclamptic female patients produced more thromboxane and less prostacyclin than that found in the normal pregnant female. Thromboxane is a potent vasoconstrictor while prostacyclin is a vasodilator; these contradictory functions contribute to reduced uteroplacental blood flow in preeclampsia [21-23].

In this study, a significant decrease in the mean of COX-2 was found between the two groups (Case and Control Group) with p-value=0.001. This means there was an anti-inflammatory effect from curcumin, The mean value of COX-2 serum in the Control Group showed a rising trend, which may lead the patient's post-birth condition to deteriorate. Preeclampsia can occur even up to six weeks after the baby's birth. Therefore, preemptive care is extremely important because there is a up to 26% risk of eclampsia seizure developing between 48-hour until 6 w after delivery. This research discovered that even at 12-hour post-surgery, a single 100 mg dose of curcumin was able to reduce the level of COX-2 serum, thus preventing the preeclamptic patients' condition from worsening i.e. developing eclampsia.

Correlation between clotting time and bleeding time at T2

There is a strong positive correlation between Clotting Time and Bleeding Time at T2, where there is a shortening of time between both of them. This result doesn't suit with the study conducted by Pan *et al.* who came to the conclusion that there was a prolongation of Clotting Time in the administration of curcumin [25]. In addition, this result also doesn't suit with the study conducted by Kim *et al.* who experienced prolongation of Bleeding Time in patients who received curcumin [26]. In this study, the results were not suit with the theory of curcumin so far that curcumin should be given carefully to patients with bleeding disorders [27].

CONCLUSION

The Case Group's Clotting Time clinically experienced a decrease, but it was statistically insignificant. On the contrary, Bleeding Time did not show any change at any point of sampling time. Thrombocyte level in the Case Group presented a clinical decrease, but statistically, it was not significant. The Case Group's COX-2 had a statistically significant decrease compared to the Control Group. The same conclusion could be derived in VAS level of the Case Group i.e. statistically insignificant reduction of VAS level. However, comparing the VAS level of the Case and that of the Control Group at T2 revealed a statistically significant difference between the two. Additionally, there was also a significant statistic correlation between Clotting Time and bleeding time at T2.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the author have contributed equally.

CONFLICT OF INTERESTS

Declared none

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