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Influence of Ozagrel Sodium along Atypical Anti-psychotic Drug on Red Blood Cell Distribution Width in Rats with Minimum and Maximum Dose Comparison

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ABSTRACT

Objective: *To study the activity of ozagrel sodium alone and in combination with the atypical antipsychotic drug on Red blood cell distribution width (RDW-CV) along with different doses and their comparison in rats.* ***Method:*** *This experimental study consisted of 120 albino rats of both gender, they were of 310-350 g, there were 10 groups which consists of each of 12 rats (n=12). Rats were treated with an accurate dose of ozagrel and atypical antipsychotic (Zuclopenthixol cis isomer of clopenthixol) alone and in combination for 3-weeks (21 days). We obtained blood sample at 0, 7th, 14th and last day of the study. Red blood distribution widths were measured from blood tests by utilizing standard medical laboratory technique. Red blood cell distribution width (RDW-CV) was measured by using the coefficient of variation indicator. Results were gathered and summarized by applying statistics. The comparison was formed between all days value to zero-day.* ***Results:*** *Minimum dose treated groups by both medications showed an increase and RDW-CV, but maximum dose showed p<0.001 decreases in RDW-CV in individual groups of drugs treatment and in case of RDW-CV maximum dose showed an increasing trend with p<0.001 in the combination groups.* ***Conclusion:*** *Maximum dose of ozagrel may cause a decrease in RDW-CV alone and it may cause an increase in (RDW-CV) with a combination of atypical antipsychotic drug.*

Keywords: Red blood cell, Width, Coefficient of variation, Ozagrel sodium, Atypical, Technique

INTRODUCTION

Blood routine is one of the normally utilized test techniques in clinical practice, in which the red blood distribution width (RDW-CV) is a significantly important thing of blood routine examination, which principally mirrors the equity of the volume and size of red blood cells. The estimation of RDW is frequently demonstrated by RDW-CV (RBC dispersion width-variety coefficient) which can be connected to the testing of various illnesses as required. Previously, RDW was essentially used to analyze various sorts of anemia, hematopoietic disturbance, intrinsic erythrocyte variations, and other blood associated diseases. In the interim, it has been step by step examined in other ailment related fields in ongoing years [1].

Red cell dissemination width (RDW) is a parameter among the variety of circling red cells. This marker exhibits the heterogeneity of red cell volume and is a part of the total blood measurement which is also called as CBC. The RDW is likewise a broadly accessible, cheap and effectively repeatable marker that estimates red platelet (RBC) volume fluctuation. Ongoing reports have exhibited that raised RDW values were identified with negative results in cardiovascular and metabolic scatters, colon malignancy and stroke-free of hemoglobin (HGB) values [2].

Raised RDW level, not NLR, might be utilized as an indicator for non-valvular AF. RDW levels were additionally associated with the rate of AF eruptions. Considering the relationship of RDW levels with hs-CRP levels, raised RDW levels may show inadequate erythropoiesis optional to unending provocative changes in AF. Planned preliminaries including micronutrients as study parameters are justified for an examination of the causal job of RDW-NLR levels in the forecast of non-valvular AF [3].

There is dependable proof which is upheld by numerous epidemiological investigations that patients with CVDs are bound to have anisocytosis and high RDW levels. While numerous clinical investigations show connections among RDW and different infection rates, seriousness, and after effects, in these examinations expressing the relationship among RDW and CVDs, there exist some unavoidable constraints [4].

Past examinations have demonstrated that RDW related to sustenance status, for example, nutrient vitamin D3, transferring and pre-albumin contrarily in HF patients. Healthful lack is another potential factor influencing the RDW level in CVDs. For example, vitamin D3 is mostly in charge of cell multiplication and erythropoiesis in the bone marrow. Practically all the vitamin D3 exists in the bone marrow, the centralization of which in marrow is in excess of 200 times more prominent than that in blood. Indeed, even a minor abatement in serum vitamin D3 levels may prompt the confusion of bone marrow erythropoiesis. In the interim, low vitamin D levels have been connected to aggravation, higher coronary artery calcium scores, weakened endothelial capacity, and expanded vascular solidness [5].

Furthermore, RDW and stroke were found in general to have a solid relationship in populace with low MCV, which proposed that a mechanism behind it could be that erythrocyte turnover moved toward becoming lower and henceforth RBC life expectancy changed [6].

An examination likewise approved the relationship between prothrombotic impacts and high RDW, which affirmed the job of RDW in cerebrovascular diseases [7].

Ozagrel sodium is an antithrombotic medication utilized in stroke. Stroke is the second commonest reason for death and the main source of inability worldwide. Approximately 87% of all strokes are the type of ischemia, because of a blockage of a course in the brain. Platelets in this way are active in the intense stage, which discharges neurotoxic and thrombogenic eicosanoids including thromboxane. There is up till now no routine viable, for the most part, acknowledged and explicit treatment for intense ischemic stroke, with the exception of aspirin. There is no solid proof on the impacts of other antiplatelet activity in intense ischemic stroke (AIS). Hence, it is important to investigate different medications with the possibility to improve the cerebral bloodstream and ensure mind work. The thromboxane A2 synthase inhibitor is a sort of intravenous antiplatelet operator. It might expand 6-keto-PGF1alpha in different disconnected cells and tissues maybe by means of gathered PG endoperoxides coming about because of the hindrance of thromboxane A2 synthase [8]. Zuclopenthixol is an entrenched thioxanthene antipsychotic. It is an atypical antipsychotic zuclopenthixol controlled examinations have demonstrated that this antipsychotic is as compelling as chlorpromazine and risperidone in the treatment of schizophrenia patients. It very well may be managed intramuscularly [9].

An anti-thrombotic/anticoagulant drug ozagrel is used as stroke treatment and zuclopenthixol which is the isomer of clopenthixol is used to treat the psychotic issues, mental disorders. These drugs can bemuse combined in co-morbidity of stroke and severe mental illness. In this study, we examined the effect of ozagrel alone and an adjunct of the atypical antipsychotic drug on Red blood cell distribution width (RDW-CV). Such type of study is important and novel to observe the severity of drug-drug interaction regarding concern parameter; it will be useful whenever these drugs will be used together.

MATERIALS AND METHODS

Statement of Ethical Approval

All conventions of this analysis and creature handlings system were done in like manner EEC board which were endorsed by Ethical advisory group of Riphah International University, through an approved number of REC/RIPS-LHR/2017/005 administered under the guideline of Institute of Laboratory Animal Resources, Commission on Life Sciences University, National Research Council (1996) which were for limiting the creature enduring.

Medications and Chemical Substances

Zuclopenthixol (ZPX) injection (Clopixol) by lundbrook Pharma, Ozagrel (OGL) injection (Ozac by Graton Pharma), Saline (Merck), Isoflurane, Vegetable thin oil, (Akhai) were purchased from the local market.

Animals for the Study

We utilized 120 rats of both genders. They were of 310-350g, we acquired 10 experimental groups in which each

gathering contained 12 rats (n=12). Treatment was begun 7 days prior, they were housed at 22 ± 2°C temperatures, 45-55% temperature and 12 hours day and light cycle in dark space of Riphah Institute of Pharmaceutical Science [10]. They were fed on free access to food and water. Duration of treatment was 21 days (3-weeks) [11]. Animals were divided into 10 groups (n=12):

- Experimental Groups: ZPX shows (Zuclopenthixol) and OGL shows (Ozagrel)
- Group I: Control oil treated group (base of ZPX)
- Group II: Control normal saline treated group (base of OGL)
- Group III: ZPX-treated group by 7.14 mg/Kg
- Group IV: OGL-treated group by 11.42 mg/Kg.
- Group V: ZPX-treated group by 28.57 mg/Kg dose
- Group VI: OGL-treated group by 22.85 mg/Kg dose
- Group VII: ZPX+OGL treated group by 7.14 mg/Kg (ZPX)+11.42 mg/Kg (OGL)
- Group VII: ZPX+OGL treated group by 28.57 mg/Kg (ZPX)+22.85 mg/Kg (OGL)
- Group IX: ZPX+OGL treated group by 28.57 mg/Kg (ZPX)+11.42 mg/Kg(OGL)
- Group X: ZPX+OGL treated group by 7.14 mg/Kg (ZPX)+22.85 mg/Kg(OGL)

Route of (ZPX) was I/m route of drug administration and Ozg (OGL) was delivered by I/p route.

Sampling of Blood

Rats were anesthetized by using the isoflurane [12]. Blood samples were collected at 0, 7^{th}, 14^{th} and 21^{st} days during the experiment. About 1 mL of blood was withdrawn at each sampling day.

Blood Analysis

Red blood cell distribution width was measured by using hematology analyzer (NORMA) with standard laboratory procedures.

Statistical Interpretation

With respect to the 0-day value of every group, percentage increase or decrease and mean with ± S.D for Red blood cell distribution width was calculated. The 2-way ANOVA was used for inferential statistics. Graphs were made by using graph pad prism version 5.0. The pattern of significant was as $p<0.05$, moderately significant was represented as $p<0.01$, and highly significant was represented as $p<0.001$.

RESULTS

Effect of Ozagrel Sodium (OGL) and Atypical Antipsychotic (Zuclopenthixol) per se and in Combination on RDW-CV(%) in Rats

Table 1 shows normal oil treated group which showed no significant change during treatment and normal saline treated group also did not show any significant change on RDW-CV values within the total duration of treatment as compared to zero-day values. This table also presents that ZPX (min) treated group showed gradually increase in RDW-CV values by $p<0.05$ at 21^{st} day, OGL (min) treated group showed significant gradual increase in RDW-CV values by $p<0.001$ at 21^{st} day, ZPX (max) treated group showed significantly decrease with $p<0.001$ at 21^{st} day, OGL (max) treated group showed decrease in RDW-CV values gradually with $p<0.001$ at 21^{st} day, ZPX (min)+OGL (min) treated group showed gradually increase in RDW-CV values with significance level $p<0.001$ at 21^{st} day, whereas ZPX (max)+OGL (max) combination group showed gradual increase in RDW-CV values with $p<0.001$ at 21^{st} day, ZPX (max)+OGL (min) combination showed gradual increase in RDW-CV values by $p<0.001$ at 21^{st} day and ZPX (min)+OGL (max) showed increase in RDW-CV values gradually by $p<0.001$ at 21^{st} day in comparison to zero-day values. Figure 1 shows the graphical expression of percentage variation in RDW-CV as compared to zero-day values.

Table 1 Effect of Ozagrel sodium (OGL) and atypical antipsychotic (zuclopenthixol) per se and in combination on RDW-CV (%) in Rats

Treatment	Treatment Days			
	0 day	7 day	14 day	21 day
Normal Oil	18.3 ± 0.2	18.4 ± 0.1	18.3 ± 0.3	18.4 ± 0.2
Normal Saline	16.2 ± 0.3	16.2 ± 0.4	16.3 ± 0.1	16.2 ± 0.1
ZPX (Min)	16.0 ± 0.7	16.4 ± 0.8	16.6 ± 0.8	16.8 ± 0.8
		↑ (2.5)	↑ (3.7)	↑ (4.8)*
OGL (Min)	15.1 ± 0.2	15.6 ± 0.2	16.4 ± 0.4	17.7 ± 0.3
		↑(3.7)	↑ (9.1)***	↑ (17.6)***
ZPX (Max)	15.1 ± 0.3	14.6 ± 0.3	13.8 ± 0.6	13.0 ± 0.5
		↓ (3.3)	↓ (8.0)***	↓ (13.7)***
OGL (Max)	18.0 ± 0.8	16.6 ± 0.5	13.8 ± 0.6	13.3 ± 0.5
		↓ (7.7)***	↓ (23.1)***	↓ (25.5)***
ZPX (Min)+OGL (Min)	18.9 ± 0.6	19.7 ± 0.6	20.1 ± 0.6	20.7 ± 1.0
		↑ (4.2)	↑ (6.7)***	↑ (9.9)***
ZPX (Max)+OGL (Max)	15.7 ± 0.1	16.5 ± 0.2	16.8 ± 0.1	18.3 ± 1
		↑(4.9)*	↑ (6.8)***	↑ (16.3)***
ZPX (Max)+OGL (Min)	14.5 ± 0.6	15.4 ± 0.77	16.36 ± 0.53	16.9 ± 0.5
		↑ (5.64)**	↑ (12.4)***	↑ (16.3)***
ZPX (Min)+OGL (Max)	17.6 ± 0.3	18.3 ± 0.2	19.06 ± 0.6	19.6 ± 0.2
		↑ (3.7)	↑ (8.1)***	↑ (11.4)***

Values are presented as Mean ± S.D, n=5. *p<0.05; **p< 0.01; *** p< 0.001; as compared to their zero day values. The values in parentheses indicate percentage change. ↑: increase , ↓: decrease

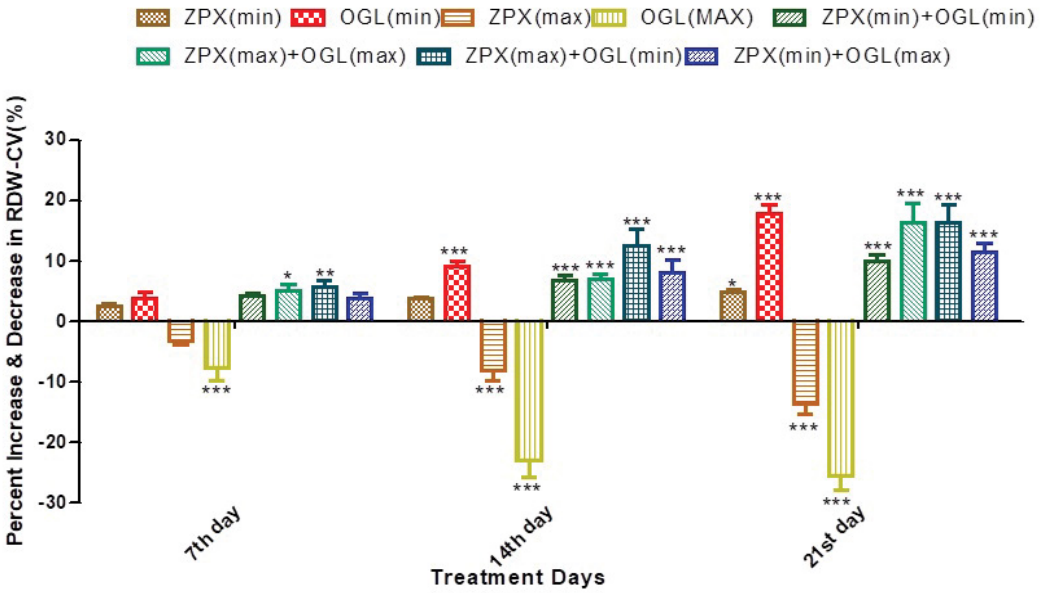

Figure 1 Effect of zuclopenthixol and ozagrel combination on RDW-CV (%). *p< 0.05, **p< 0.01, ***p<0.001 as compared to their zero day values

DISCUSSION

RDW-CV values were decreased by both drugs individually but significant increase had been observed by combination therapy with maximum dose and less increase with minimum dose groups. Chance of such results might be associated with hemoglobin and mean corpuscular volume due to the relationship of these parameters with RDW. Increasing results on RDW in this study was supported by another research work regarding antithrombotic activity, in which under the influence of antithrombotic drug increase in RDW were observed [13]. Increase the size of RDW minimum

dose of antipsychotic also supported by a previous study in which the researcher presented that RDW values are increased after treatment with an antipsychotic drug. This was predictable with the examination directed in research who found that an expansion in cytokines as a fiery factor was emphatically related with the restraint of erythrocyte development by erythropoietin, which was reflected by an expansion in the RDW esteem [14]. Maximum doses of these drugs significantly decrease, it may be associated with the toxicity of maximum dose regarding hemoglobin deficiency with maximum dose. There is a need in the future to find a mechanism behind the opposite results of the maximum dose in comparison of minimum dose.

CONCLUSION

Maximum dose of ozagrel may cause a decrease in RDW-CV alone and it may cause an increase in (RDW-CV) with a combination of atypical antipsychotic drug and alone in minimum dose. Therapeutic drug monitoring regarding this parameter of hematology is much important during treatment with these drugs.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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