Original Research Article

Cardiotoxicity among patients using Pertuzumab, Trastuzumab, and Taxane with HER2-Positive Early-Stage Breast Cancer: A Single Centre Experience

Running Title: Cardiotoxicity of anti- HER2 in early-stage breast cancer

Abstract

Aim: The current study aimed to investigate the incidence rate, risk factors,and mortality in Early- Stage Breast Cancer patients using anti-HER2 treatment.

Patients and methods: A total of (106) patients diagnosed with HER2 positive early-stage breast cancer receiving anti-HER2 treatment at KAMC from 2015 to 2019 were included in the analysis to assess the incidence of cardiotoxicity was collected as a retrospective study. Univariate and multivariate analyses were conducted to understand the relation of the LVEF and treatment combinations, and comorbidities. Multiple exact logistic regression analysis was done to understand the relationships.

Results

The median age of the study participants was 50 years. The results suggest 42.45%, selected study participants (n=45) were at the postmenopausal stage, and 33.96% (n=36) and 23.58% (n=25) patients were at the premenopausal and perimenopausal stages, respectively.Among all, 50.94% (n=54) of the patients were either overweight or obese. Altogether, 30.19% of the patients (n=32) were having comorbidities. Among them, 19.81% were having hypertension, 9.43% were having dyslipidemia, 8.9% were having osteoporosis, 16.98% were having diabetes mellitus, and 5.66% were having cardiovascular diseases. The majority of the patients (66.05%) had estrogen-positive reports, followed by progesterone positive (50%). Results suggest, the more the drug combination, the higher the odds ratios for the declined ejection fraction patient group. Further, patients treated with pertuzumab and trastuzumab combination were four times more likely to have a decline in their ejection fraction compared to those who did not use pertuzumab and trastuzumab drug combination (OR 4.28, 95% CI (1.68-10.91)).

Conclusion

The present study demonstrated that the drug combination considered in this study is associated with reduced Left Ventricular Ejection Fraction (LVEF)and similarly comorbidities were also related to the ejection fraction.However, a larger study in a global patient population will confirm the present observations.

Keywords: HER2,cardiotoxicity,breast cancer, chemotherapy, left ventricular ejection fraction.

1. Introduction

Cancer is the most prevalent cause of death globally among non-communicable diseases. Breast cancer is the second most common form of cancer [1,2]. Breast cancer is categorized based on its etiology, molecular features, clinical conditions, and other factors. For clinical diagnosis and treatment, breast cancer is largely classified according to the receptors such as estrogen receptor, progesterone receptor, and human epidermal growth factor 2 (HER2) receptors. The prevalence of specific hormone receptor-based breast cancer varies globally. Reports suggest such variation of the receptor(estrogen/progesterone) positive or negative varies depending on the geographical region and ethnic groups [3,4]. Breast cancer is the most diagnosed cancer in women in Saudi Arabia [2]. The mortality rate due to breast cancer is high and is having an increasing trend [5]. In 2020, the estimated diagnosed breast cancer patients were 2.3 million with a global death toll of 6,85,000.The scenario is not different in Saudi Arabia. Breast cancer is a common malignancy among Saudi females,with a prevalence of 21.8%. The most recent study of cancer-related mortality among Saudi women finds that breast cancer is the ninth leading cause of death [6-8]. According to the Saudi Cancer Registry of the King Faisal Specialist Hospital and Research Centre, around 930 new cases of breast cancer are diagnosed each year in Saudi Arabia. In 2010, out of 5,378 cancer diagnoses in SaudiArabia,1,473(27.4%) were for breast cancer, making it the most common newly diagnosed cancer among women [9].

Clinical trials demonstrated that the combination of taxanes with trastuzumab and pertuzumab targeted therapy of HER2 significantly improves the overall response rates and survival as a first-line therapy followed by pertuzumab and trastuzumab as maintenance therapy. However, many clinical studies have reported that cardiac adverse events such as decreased ejection fraction and heart failure adverse effects associated with the use of this combination, the large benefit of this targeted therapy warrants its use in most breast cancer cases with close monitoring of cardiac functions.

Trastuzumab as monotherapy is associated with cardiotoxicity, but the exact mechanism of toxicity remains unknown. In patients with a normal left ventricular function before starting trastuzumab therapy risk of heart failure is low.

Cardiac adverse events like decreased ejection fraction and heart failure have been of specific concern in patients with HER2+ breast cancer. Further studies that carefully focus on evaluating and monitoring the incidence of cardiotoxicity are highly required to guide early management and/or improve the outcomes.

Studies of patients treated for the active disease with reduced cardiac function at baseline have reported serious adverse events attributable to HER2-directed therapy. We have estimated the incidence and associated risk factors of cardiotoxicity effects from anti-HER2 treatment among all patients treated HER2 positive early-stage breast cancer at a single center.

2. Methods

2.1. Study design

The present single-site retrospectivestudy was designed to understand and evaluate the incidence of cardiotoxicity in early breast cancer patients who were receiving anti-HER2 medications such as pertuzumab, trastuzumab, and taxane. An extensive assessment was done for possible risk factors associated with the early breast cancer patients who underwent anti-HER2 treatment (Figure 1).

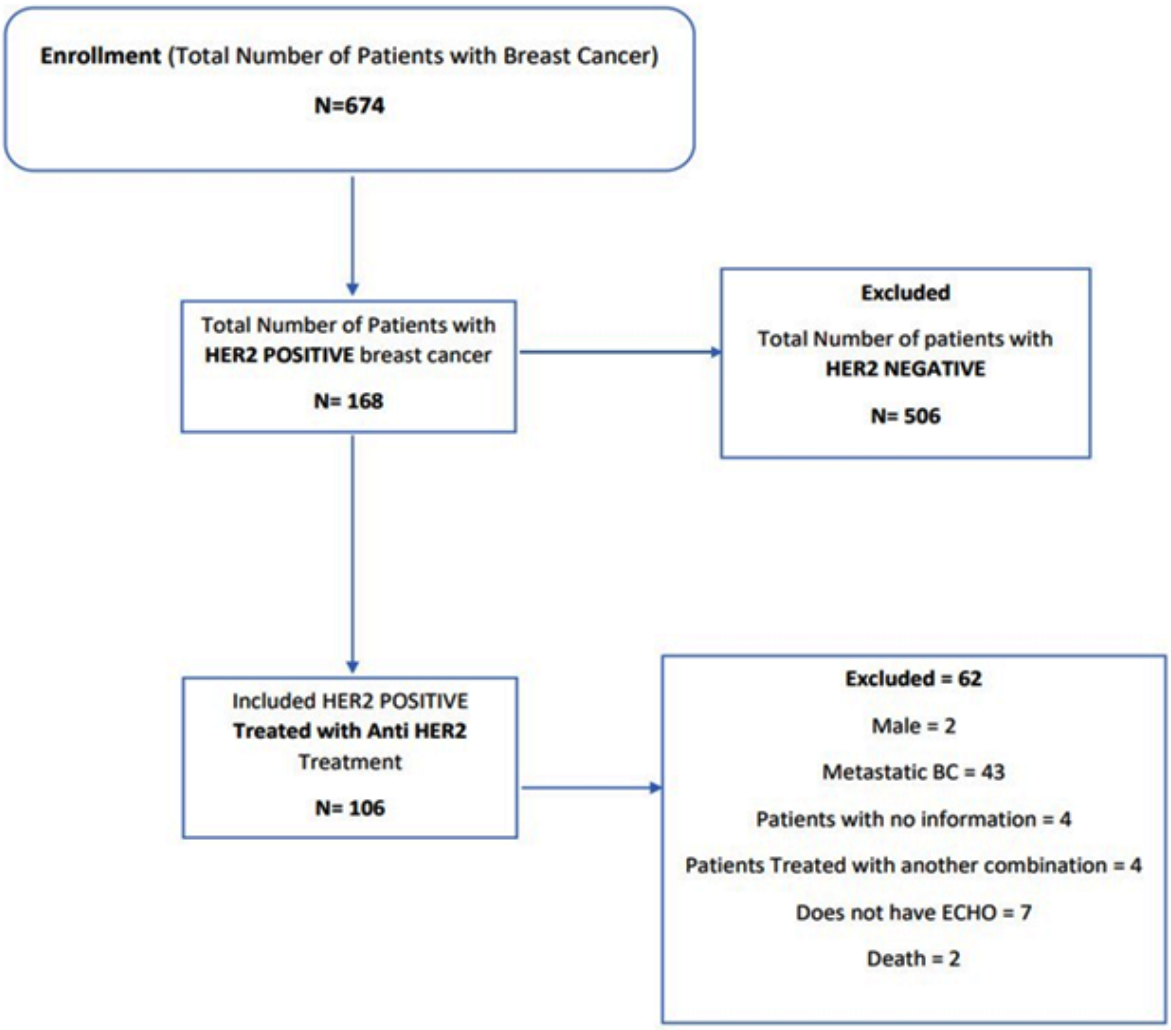

Figure1: Patient enrolment, screening, inclusion, and exclusion in the study

2.2. Study location and duration

The study was conducted at King Abdulaziz Medical City(KAMC), Jeddah, Saudi Arabia. The data was considered for the breast cancer patients for five years altogether in this treatment center and information related to the patients was collected from January 2015 to December 2019. Patient selection was done strictly following the approved eligibility criteria following the study design and protocol.

2.3. Patient and Inclusion criteria

The study design contains precise inclusion and exclusion criteria for the patient population selection. During the patient selection, each report of the prospective patients was carefully reviewed by the study investigator. Every patient in this study underwent a left ventricular ejection fraction (LVEF) measurement using an echocardiography method at the baseline (before any treatment) and during the anti-HER2 therapy. According to the instruction of the International Agency for Research on Cancer, Saudi Arabia, the estimated age-standardized incidence rate (ASIR) for breast cancer was 22.4 per 100,000 women in 2008 [10]. In the present study, the patients' age was considered following the IARC recommendations.

Adult patient aged >=22.4was only considered to be eligible to participate in this study. Confirmation from the medical reports was obtained for each case regarding the HER2 positive early-stage breast cancer for the study population. Patients who were undergoing treatment within 2015 and 2019, and were having required medical records were only eligiblefor this study. It was carefully observed during the medical record assessment that patients were being treated with specific therapeutic agents including pertuzumab, trastuzumab, and taxane.

During the screening stage patients with HER2-negative reports were excluded from the study. Alongside, patients who did not meet the inclusion criteria mentioned earlier such as patients having metastatic breast cancer, male cancer patients, undergoing other radiation and chemotherapeutic treatments were also excluded from the study.

2.4. Cardiotoxicity consideration and evaluation

Apart from the mentioned criteria, cardiotoxicity was keenly investigated for each report during patient selection. The condition of cardiotoxicity was considered as 1) reduction of LVEF, either global or specific in the interventricular septum; 2) symptoms or signs associated with heart failure (HF); 3) reduction in LVEF from baseline values to 5%- <55% in presence of signs or symptoms of HF; reduction in LVEF ≥10%-<55% without signs or symptoms of HF. Specifically, a 1% decline from the basal reading of ejection fraction (EF) was considered as the presence of cardiotoxicity incidence.

2.5. Ethical approval and other parameters

Appropriate ethical approval was obtained from the Institutional Review Board (No: SP21J/048/03). The parameters that were considered for the study included Left Ventricular Ejection Fraction percentage at pre-and-post treatment stages, menopausal state, BMI, hormone receptor status, and stage of the disease. Additionally, associated comorbidities were also considered such as cardiovascular risk factors, hypertension, coronary artery disease, congestive heart failure, kidney disease, diabetes mellitus, and any other comorbidities.

2.6. Statistical Analysis

A detailed descriptive analysis was conducted for the obtained patient data. All categorical data were expressed as percentages and numerical data were presented as mean(±SD). We conducted Chi-square ($\chi 2$) tests and Fisher exact tests for less frequent (<5) samples to compare between the patients with and without declined ejection fraction (EF). Multiple exact logistic regression with a standard maximum-likelihood-based estimator was applied to examine the association between the declined ejection fraction and applied medications. All statistical tests were conducted two-tailed, and findings were considered statistically significant at $P < 0.05$. All analyses were conducted using SAS statistical software (version 9.4, SAS Institute Inc. Cary, NC).

3. Results

3.1. Patient screening and demographic analysis

The initial patient enrolment was having 674 patients altogether. However, due to strict inclusion and exclusion criteria, the final dataset contained 106 patients (Figure1). The median age of the patients was 50 years. The age range of the patients was between 27 years and 89

years (Table1).

3.2. Menopausal stage

It was observed that almost half of the selected study participants(42.45%, n=45) were at the postmenopausal stage. On the other hand, 33.96% (n=36) and 23.58% (n=25) patients were at the premenopausal and perimenopausal stages, respectively (Table 1).

3.3. Obesity and comorbidity

It was noted that 50.94% (n=54) of the patients were either overweight or obese (Table1). Evaluation of the comorbidities suggested that 30.19% of the patients (n=32) were having comorbidities.Assessment of the comorbidities revealed that the patients were having hypertension (19.81%, n=21), dyslipidemia (9.43% n=10), osteoporosis (8.9%, n=9), diabetes mellitus (16.98%, n=18), and cardiovascular complications (5.66%, n=6) (Table1). Among the comorbidities, hypertension and diabetes mellitus were observed to be prevalent among the study population.

Our observation suggested asignificant (P<0.0001) presence of comorbidities among declined ejection fraction (35.42%) patient group compared to the non-decline ejection fraction patient population (25.86%).

3.4. Hormonal status

All the patients were examined for the presence of specific hormonal receptors. Progesterone and estrogen receptor presence was investigated. The majority of the patients (66.05%, n=70) had estrogen-positive reports, followed by progesterone positive (50%, n=53), progesterone negative (49.06%, n=52), and estrogen negative (33.02%, 35%). Only two patients did not show any positive or negative results for the progesterone or estrogen receptor presence.

3.5. Medication after diagnosis

Most of the patients (97.17%, n=103) were receiving trastuzumabtaxol as a treatment for early-stage breast cancer for HER-positive patients, followed by Taxol (92.45%, n=98), and pertuzumab (53.77%, n=57) (Table1).A statistically significant difference among the patients treated with pertuzumab (P 0.001), a combination of pertuzumab and trastuzumab (P 0.001),and a combination of pertuzumab, trastuzumab, and taxol (P 0.0008) were observed for the declined and non-declined ejection fraction patient groups in univariate analysis (Table 1, Figure 2).

Table 1: Baseline demographic and clinical characteristics for early stages female breast cancer patients at NGHA,Jeddah.

Parameter	Patients' characteristics	P-value
	n (%)[1]	
Total		
Median age (range)	50 (27-89)	<.0001[2]
BMI		0.84[3]
Non-obese	52	

Overweight/obese	54	
Comorbidity		<.0001
Yes	32	
No	74	
Hypertension		<.0001
Yes	21	
No	85	
Dyslipidemia		<.0001
Yes	10 (9.43)	
No	96	
Osteoporosis		<.0001
Yes	9	
No	97	
Diabetes Mellitus		<.0001
Yes	18	
No	88	
Cardiovascular Disease		<.0001
Yes	6	
No	100 (94.34)	
Medication after Pertuzumab		0.43
Yes	57	
No	49	
Taxol		<.0001
Yes	98	
No	8	
Trastuzumab Taxol		<.0001
Yes	103	
No	3	
Menopausal status		0.05
Perimenopause	25	
Postmenopausal	45	
Premenopausal	36	
Estrogen receptors (ER)		<.0001
Positive	70	
Negative	35	
NA	1 (0.94)	
Progesterone receptors (PR)		<.0001
Positive	53 (50)	
Negative	52	
NA	1	

[1] n= sample size in percentage (%),t-test used for continuous variable

[2] T-test was applied for continuous variables.

[3] Fisher's Exact test was applied for <5 sample frequency and Chi-square (X^2) test for > 5 sample frequency.

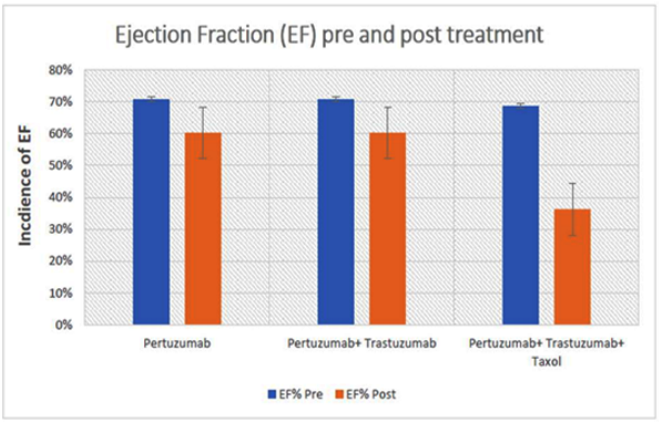

Figure 2: A comparative presentation of ejection fraction (EF) at pre-and-post treatment using pertuzumab, a combination of pertuzumab and trastuzumab, and a combination of pertuzumab, trastuzumab, and taxol.

In multivariate analysis, there were statistically significant associations between pertuzumab (OR 3.52, 95% CI (1.5-8.22)) and its combinations pertuzumab and trastuzumab (OR 4.28, 95% CI (1.68, 10.91)); and pertuzumab, trastuzumab, and taxol (OR 4.56, 95% CI (1.8, 11.54)). Patients treated with pertuzumab had thrice the odds ratio for the declined ejection fraction patient group (OR 3.52, 95% CI (1.5-8.22)). It was further observed that the more the drug combination, the higher the odds ratios for the declined ejection fraction patient group (Table 2). Moreover, we noted that the patients treated with pertuzumab and trastuzumab combination were four times more likely to have a decline in their ejection fraction compared to those who did not use pertuzumab and trastuzumab drug combination (OR 4.28, 95% CI (1.68-10.91)). A similar trend was observed for the patients treated with an additional combination of pertuzumab, trastuzumab, and taxol (Table 2).

Table 2: Risk factors associated with a decline inejection fraction(EF) for early stages female breast cancer patients at NGHA, Jeddah

	Baseline declined ejection fraction	**Declined ejection fraction Pre vs. Post**	**P-value**
	n (%)	**OR (95%CI)**	
Age groups			0.13
27-50	50 (47.17)	Ref	
51-8	56 (52.83)	2.03 (0.79, 5.21)	
Comorbidity			0.08
Yes	32 (30.19)	2.38 (0.88. 6.41)	
No	74 (69.81)	Ref	
Pertuzumab			0.003
Yes	57 (53.77)	3.52 (1.5, 8.22)	
No	49 (46.23)	Ref	
Pertuzumab+ Trastuzumab			0.002
Yes	57 (53.77)	4.28 (1.68, 10.91)	
No	49 (46.23)	Ref	
Pertuzumab+Trastuzumab+Taxo			0.001
Yes	54 (50.94)	4.56 (1.8, 11.54)	

No	52 (49.06)	Ref	
Progesterone receptors (PR)			0.48
Positive	53 (50)	0.59 (0.25, 1.38)	
Negative	52 (49.06)	Ref	
NA	1 (0.94)	0.01 (0.02, 1.88)	

1 Odds ratio and confidence interval was calculated using exact multiple logistic regression.

2 Reference = Ref.

3 "NA" Not available.

The pre-and-post comorbidity comparison (Figure 3) suggested that there was a significant difference in ejection fractions for hypertension, dyslipidemia, diabetes mellitus, and cardiovascular disease.

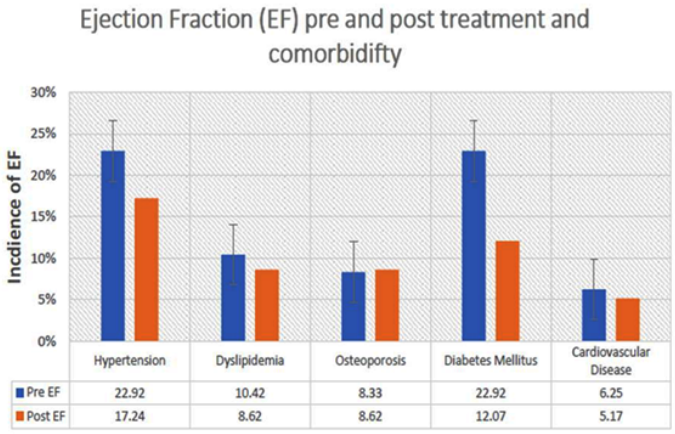

Figure 3: A comparative presentation of ejection fraction (EF) with reference to different comorbidities

4. Discussion

Cancer has emerged as a curse to human society in the present century, taking a toll on millions of lives irrespective of geographical region, gender, and age. Breast cancer's global prevalence is on the rise and is presently the second most common cancer in the world[1]. Several factors are found to be responsible for inducing or promoting breast cancer which are categorized as hereditary factors, demographic factors, reproductive factors, hormonal factors, breast associated factors, and lifestyle associated factors [1]. However, no linear association or relationships of these factors altogether are established either to induce or aid in progressing breast cancer. Although the relation or influence of individual factors is known in many cases,their collective impact is yet to be discovered.

The advancement of medical science saved millions of lives in this century by applying some wonder live-saving drugs. For HER2-positive breast cancer trastuzumab, pertuzumab, and taxol are being used for decades all over the world [11]. As a first-line treatment, these drugs were successful in improving the time required for disease progression, response time, specific targeting to solid tumors, and the time required for treatment failure [12].

These drugs are used in different combinations as part of the chemotherapy depending on the diagnosis[13]. Such combination therapy also demonstrated improvement in the overall

survival of the patient [12]. Over the decades, the usage of pertuzumab, trastuzumab, and taxol has increased as potential reliable therapeutic agents for breast cancer treatment and are being used in different ways on a case-by-case basis [14,15]. These drugs have helped many patients to survive longer and combat the disease using pertuzumab, trastuzumab, and taxol as part of the first-line chemotherapeutic treatment for HER2 positive early-stage breast cancer.Trastuzumab, a monoclonal antibody used for HER2-positive breast cancer remains the gold standard of treatment so far [16].

However, side effect prevention has been a concern for the application of these chemotherapeutic agents [17]. Most of the reported side effects are infusion-related such as fever and chills. Apart from this, there is a range of mild to moderate adverse responses recorded that included myalgia, diarrhea, haematotoxicity, infections, rash, arthralgia, and others [18-20].

Cardiotoxicity has been a serious concern regarding the use of these drugs.A serious adverse event, symptomatic heart failure is reported in 1-4% of the patients,and association of the LVEF was also noted.In most of the cases, the cardiological events were reversible and temporary, discontinuation of the therapeutic agent improved the condition[21]. Ewer and Ewer argued thatthe cardiotoxicity-related alteration due to the use of trastuzumab may have microscopic ultrastructural changes in the heart muscles which are partially reversible after the discontinuation of the medication [22]. However, in most of the reports related to the cardiotoxicity-related issues due to the usage of trastuzumab, it was suggested that it was anthracycline-induced majorly and the trastuzumab-induced cardiac changes are reversible [23]. Several recent reports suggested multiple ways to tackle such cardiotoxicity [24,25].

In the present study, we have witnessed the induction of cardiotoxicity in the patients of early-stage breast cancers who are availing treatments with various combinations of the pertuzumab, trastuzumab, and taxol. Our results are statistically significant and are as per the reports related to cardiotoxicity associated with these drugs.Another report also suggested the association of cardiotoxicity due to the treatment with trastuzumab and pertuzumab combination earlier [26]. Recently, Abdel-Razaq et al. reported that 90% of the HER2 positive breast cancer patients showed cardiotoxicity which was trastuzumab induced in Saudi Arabia [27]. Similar to our observations, Abulkhair and colleagues reportedtrastuzumab-associated cardiotoxicity in HER2 positive breast cancer patients in a single institution-based retrospective study [28]. Another single-center study reported persistent low LVEF during follow-up in the majority of the patients due to drug-induced cardiomyopathy from the Saudi Arabia region [29].It was observed in this study that reduction of left ventricular ejection fraction is associated with the increasing combination of the pertuzumab, trastuzumab, and taxol. Moreover, associations with comorbidities were also observed for the present study population.

Caron and Nohria recommended categorizing the high-risk HER2-positive breast cancer patients who may show association with cardiotoxicity due to therapeutic effects and considering modified treatment regimessuch as the use of Anthracycline-free treatment regime, dose reduction, and other possibilities to avoid cardiotoxicity [30].

5. Recommendation

However, further larger multicenter-based studies are essential to understand establish the cardiotoxicity effect of trastuzumab, pertuzumab, and taxol. Diverse patient population, more number of drug combinations. Longer duration study and attention to individual comorbidity

may help in understanding the relation of cardiotoxicity during the use of these chemotherapeutic agents.

6. Conclusion

In the present study, we have observed a statistically significant association of reduced left ventricular ejection fraction and various combinations of pertuzumab, trastuzumab, and taxol. Association of comorbidities and LVEF reduction were also found associated with the present HER2 positive early-stage breast cancer patient population.

Consent (If applicable): Not applicable

Ethical Approval: Not applicable

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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