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Meta-Analysis for Naproxen Bioquivalence Studies

Naproksen Biyoeşdeğerlik Çalışmaları İçin Meta Analizi

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ABSTRACT Objective: Interchangeability between generic drugs is required for switching a patient from one generic drug to another. For this purpose, meta-analysis is used between generic drugs based on data obtained from independent bioequivalence studies. **Material and Methods:** From 2005 to 2013, Naproxen pharmacokinetic data of clinical trials done by Novagenix Bio Analytical R&D Centre in Turkey were used. Seven studies were suitable for the criteria of meta-analysis. The 90% confidence intervals for the differences between the means of pharmacokinetic parameters, area under the curve ($AUC_{0\text{-}tlast}$) and maximum plasma concentration (C_{max}), were determined for each binary combinations of seven generic drugs by meta-analysis used in average bioequivalence. **Results:** Considering the 90% confidence intervals, 76.2% of the binary combinations for only C_{max} and 66.7% of the binary combinations for only $AUC_{0\text{-}tlast}$ have been concluded as bioequivalent. 47.6% of the binary combinations have been fulfilled the bioequivalence criteria for both C_{max} and $AUC_{0\text{-}tlast}$. **Conclusion:** Since some of the generic drug combinations may not match the bioequivalence acceptable range, switching a patient from one generic drug to another is leading to a major safety concern.

Keywords: Meta-analysis; generic drug; interchangeability

ÖZET Amaç: Bir hastanın bir jenerik ilaçtan diğerine geçişi için jenerik ilaçlar arasında değiştirilebilirlik gereklidir. Bu amaç için, jenerik ilaçlar arasında bağımsız biyoeşdeğerlik çalışmalarından elde edilen veriye dayalı meta analizi kullanılmaktadır. **Gereç ve Yöntemler:** 2005 yılından 2013 yılına kadar Türkiye'deki Novagenix Bioanalitik İlaç Ar-Ge Merkezi'nde analizlenen ve raporlanan Naproksen biyoeşdeğerlik çalışmalarının verisi kullanılmıştır. Meta analizinin kriterlerine uygun yedi çalışma vardır. Ortalama biyoeşdeğerlikte kullanılan meta analizi ile bu yedi jenerik ilacın ikili kombinasyonlarının farmakokinetik parametreleri için, eğri altındaki alan (EAA) ve maksimum plazma konsantrasyon (C_{maks}), ortalamalar arasındaki farkın %90 güven aralıkları elde edilmiştir. **Bulgular:** %90 güven aralığı göz önüne alındığında, sadece C_{maks} için ikili kombinasyonların %76.2'si ve sadece $EAA_{0\text{-}tlast}$ için ikili kombinasyonların %66.7'si biyoeşdeğer olarak sonuçlanmıştır. İkili kombinasyonların %47,6'sı, hem C_{maks} hem de $EAA_{0\text{-}tlast}$ için biyoeşdeğerlilik kriterlerini yerine getirmiştir. **Sonuç:** Jenerik ilaç kombinasyonlarının bazıları biyoeşdeğerlik kabul limitlerini karşılayamayabildiğinden, bir hastanın bir jenerik ilaçtan diğerine geçişi büyük bir güvenlik endişesine sebep olmaktadır.

Anahtar Kelimeler: Meta analizi; jenerik ilaç; biyoeşdeğerlik

When a brand-name drug is going off patent protection, the innovative drug companies and/or generic drug companies may file an abbreviated new drug application (ANDA) for generic approval through the conduct of the bioequivalence study. Bioequivalence testing for generic approval is based on the Fundamental Bioequivalence Assumption that when two drug products have similar

drug absorption profiles (or equivalent in average bioavailability), it is assumed that they will reach similar therapeutic effects or they are therapeutic equivalent.[1]

Although each generic copy of the brand-name drug can be used as a substitute for the brand-name drug, Food and Drug Administration (FDA) does not indicate that these generic copies of the same brand-name drug can be used interchangeably. It is therefore important to investigate the overall bioequivalence and inconsistencies among all generic copies of the same brand-name. For this purpose, Chow and Liu (1997) proposed the concept of meta-analysis for the post-approval bioequivalence review.[2]

The idea of meta-analysis is to provide an overview of bioequivalence among generic drugs based on data from independent bioequivalence trials (or submissions). The purpose is not only to assess a bioequivalence among generic drugs of the same brand-name drug but also to provide a tool to monitor the performance of the approved generic copies of the same brand-name drug. In Chow and Liu's approach, the assumption of having the same inter-subject and intra-subject variances for all studies, which limits its practical use, is rather restricted but strong. To overcome this problem, Chow and Shao (1999) proposed an alternative method for meta-analysis that relaxes this assumption. The proposed alternative meta-analysis increases the statistical power when the inter-subject variability is not too large.[3]

Thus, in this study, interchangeability between different generic drugs was analysed using this alternative method. A systematic bioequivalence review was conducted with several studies containing Naproxen, analysed and reported by Novagenix Bio Analytical R&D Centre.

MATERIAL AND METHODS

The comparative bioavailability assessment of two or more formulations of the same active ingredient to be administered by the same route is termed bioequivalence. Bioequivalence studies compare both the rate and extent of absorption of generic (test) drug with the brand-name (reference) drug. The drug concentration -time curve is generally used to assess the rate and extent of absorption. If two formulations exhibit similar drug concentration-time profiles in the blood/plasma, they should exhibit similar therapeutic effects.[4]

To investigate bioequivalence, the pharmacokinetic (PK) parameters to be analysed are the area under the concentration-time curve from zero to the last measurable concentration ($AUC_{0\text{-}tlast}$,), reflecting the extent of exposure, and the maximum plasma concentration (C_{max}), reflecting the rate of exposure. In order to achieve a better approximation to a normal distribution, the data should be transformed prior to analysis using a logarithmic transformation. For these parameters the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80.00-125.00%.[5]

For average bioequivalence, a standard two-sequence, two-period crossover study is usually employed. Let y_{ijk} be the original or the log-transformation of the pharmacokinetic response of interest [e.g., $AUC_{0\text{-}tlast}$ and C_{max}] of the ith subject in the jth period and kth sequence of the trial. The following statistical model is assumed:

$$y_{ijk} = \mu + F_l + P_j + Q_k + S_{ikl} + e_{ijk} \quad (1)$$

where μ is the overall mean; P_j is the fixed effect of the jth period (j= 1, 2, and $P_1+P_2 = 0$); Q_k is the fixed effect of the kth sequence (k= 1, 2, and $Q_1+Q_2 = 0$); F_l is the fixed effect of the lth drug formulation when j= k, l =T, test formulation; when $j \neq k$, l=R, the reference (brand-name) formulation ($F_T+F_R = 0$); S_{ikl} is the random effect of the ith subject in the kth sequence under drug formulation l; and S_{ik}= (S_{ikT}, S_{ikR}), i= 1, . . . , n_k, $_k$= 1, 2, are independent and identically distributed (i.i.d.) bivariate normal random vectors

with mean 0 and variance σ_S^2; e_{ijk}'s are independently distributed with mean 0 and variance σ_e^2. S_{ik}'s and e_{ijk}'s are mutually independent.[6]

To apply the meta-analysis methodology, we selected naproxen active ingredient bioequivalence studies, analysed and reported by Novagenix, that have the following conditions:

I. The same sample size,

II. The same study design as two sequences and two-period crossover design,

III. Confidence intervals within the bioequivalence limits,

IV. The same brand-name drug in different batch numbers.

From 2005 to 2013, nine naproxen active ingredient bioequivalence studies have been performed in Novagenix. Seven of them provide the above conditions and included in the meta-analysis.

The identity of the Sponsor and brand-name drug manufacturers was protected.

For meta-analysis between generic drugs, the method proposed by Chow and Shao in bioequivalence studies was applied. A 90% confidence interval for the difference of the means of C_{max} and $AUC_{0\text{-tlast}}$ were constructed for each possible binary combination of the generic drugs to assess the interchangeability between them.

Suppose that there are H independent bioequivalence studies. An additional subscript, *h*, is added to the responses so that y_{ijkh} is the observation as defined in model (1) but it is from the *h*th bioequivalence study.

To assess two test drugs' (generic copies) bioequivalence, say *h* and h ′,

$$\tilde{\delta}_h - \tilde{\delta}_{h'} = \bar{y}_{Th} - \bar{y}_{Th'},$$

where $\bar{y}_{Th} = (\bar{y}_{11h} + \bar{y}_{22h})/2$.

The method is divided into classes according to whether the sample size of sequences (n_{kh}) is small or large and equal. Since sample sizes of sequences of Naproxen bioequivalence studies are small and equal, the exact method shown below was applied.

Since $n_{kh} = n_{kh'}$, $k = 1, 2$, $c_h = c_{h'}$ whereas $c_h = \frac{1}{4}\left(\frac{1}{n_{1h}} + \frac{1}{n_{2h}}\right)$. Define

$$d_{i1hh'} = y_{i11h} - y_{i11h'}, \text{ i=1,...,n}_{1h}, \quad (2)$$

$$d_{i2hh'} = y_{i22h} - y_{i22h'}, \text{ i=1,...,n}_{2h}. \quad (3)$$

Let $s^2_{khh'}$ be the sample variance based on $\{d_{ikhh'}, \text{ i=1,..., n}_{kh}\}$, k=1, 2 and

$$s^2_{hh'} = \frac{(n_{1h} - 1)s^2_{1hh'} + (n_{2h} - 1)s^2_{2hh'}}{n_{1h} + n_{2h} - 2}$$

Then an exact 90% confidence interval for $\delta_{hh'}$ is

$$\tilde{\delta}_h - \tilde{\delta}_{h'} \pm t_{.05}(n_{1h} + n_{2h} - 2)\sqrt{2c_h s^2_{hh'}} \quad (4)$$

A *Chi*-square test with H-1 degrees of freedom was applied to test the null hypothesis of homogeneity of the reference products among the studies as a prerequisite to combine data to perform meta-analysis.

The calculations required for the meta-analysis were performed using the Microsoft Excel 2010®.

RESULTS

Seven naproxen bioequivalent studies that have the same reference drugs of different batches were selected and analysed for the meta-analysis.

The 90% confidence intervals of the differences of means between the binary combinations of test drugs from 1 to 7, for C_{max} and $AUC_{0\text{-}tlast}$ were calculated and shown in Tables 1 and 2, and Figures 1 and 2, respectively.

TABLE 1: Confidence Intervals and Conclusion of the Binary Combinations of Test Drugs in the Meta-Analysis for C_{max}.

Combinations	Mean* of Test *h*	Mean* of Test *h'*	D*	Var(D)*	Ratio**	Lower Limit of 90% CI**	Upper Limit of 90% CI**	Confirmation of BE
Test 1 x Test 2	4.38147	4.30698	0.07449	0.04698	107.73370	94.96607	122.21788	Yes
Test 1 x Test 3	4.38147	4.30926	0.07221	0.05995	107.48828	93.21376	123.94876	Yes
Test 1 x Test 4	4.38147	4.32642	0.05505	0.03513	105.65966	94.74030	117.83754	Yes
Test 1 x Test 5	4.38147	4.31163	0.06984	0.03342	107.23347	96.41101	119.27078	Yes
Test 1 x Test 6	4.38147	4.42056	-0.03909	0.05994	96.16634	83.39552	110.89282	Yes
Test 1 x Test 7	4.38147	4.27707	0.10440	0.02949	111.00468	100.44677	122.67233	Yes
Test 2 x Test 3	4.30698	4.30926	-0.00228	0.04308	99.77219	88.42064	112.58108	Yes
Test 2 x Test 4	4.30698	4.32642	-0.01944	0.04682	98.07485	86.47086	111.23603	Yes
Test 2 x Test 5	4.30698	4.31163	-0.00465	0.04156	99.53567	88.39996	112.07414	Yes
Test 2 x Test 6	4.30698	4.42056	-0.11358	0.05311	89.26300	78.05924	102.07483	No
Test 2 x Test 7	4.30698	4.27707	0.02991	0.03819	103.03617	91.95963	115.44687	Yes
Test 3 x Test 4	4.30926	4.32642	-0.01716	0.04054	98.29878	87.42965	110.51914	Yes
Test 3 x Test 5	4.30926	4.31163	-0.00237	0.05824	99.76294	86.69101	114.80596	Yes
Test 3 x Test 6	4.30926	4.42056	-0.11130	0.07664	89.46681	76.15424	105.10657	No
Test 3 x Test 7	4.30926	4.27707	0.03219	0.03126	103.27143	93.17427	114.46280	Yes
Test 4 x Test 5	4.32642	4.31163	0.01479	0.02700	101.48950	92.23442	111.67326	Yes
Test 4 x Test 6	4.32642	4.42056	-0.09414	0.06830	91.01518	78.17375	105.96605	No
Test 4 x Test 7	4.32642	4.27707	0.04935	0.02612	105.05871	95.62853	115.41882	Yes
Test 5 x Test 6	4.31163	4.42056	-0.10893	0.07291	89.67941	76.63831	104.93963	No
Test 5 x Test 7	4.31163	4.27707	0.03456	0.02896	103.51682	93.75611	114.29370	Yes
Test 6 x Test 7	4.42056	4.27707	0.14349	0.07952	115.42987	97.95989	136.01541	No

*: Logarithmic scale **: Original scale

$$D = \tilde{\delta}_h - \tilde{\delta}_{h'}$$

TABLE 2: Confidence Intervals and Conclusion of the Binary Combinations of Test Drugs in the Meta-Analysis for $AUC_{0\text{-tlast}}$.

Combinations	Mean* of Test *h*	Mean* of Test *h'*	D*	Var(D)*	Ratio**	Lower Limit of 90% CI**	Upper Limit of 90% CI**	Confirmation of BE
Test 1 x Test 2	7.21190	7.05008	0.16182	0.05200	117.56535	102.95464	134.24954	No
Test 1 x Test 3	7.21190	7.04787	0.16403	0.04196	117.82515	104.58446	132.74214	No
Test 1 x Test 4	7.21190	7.12940	0.08250	0.04788	108.60039	95.61524	123.34901	Yes
Test 1 x Test 5	7.21190	7.02663	0.18527	0.08360	120.35427	101.71460	142.40975	No
Test 1 x Test 6	7.21190	7.12486	0.08704	0.03852	109.09425	97.31845	122.29495	Yes
Test 1 x Test 7	7.21190	7.02326	0.18864	0.07313	120.76072	103.17605	141.34239	No
Test 2 x Test 3	7.05008	7.04787	0.00221	0.03544	100.22098	89.82107	111.82503	Yes
Test 2 x Test 4	7.05008	7.12940	-0.07932	0.05167	92.37449	80.92793	105.44006	Yes
Test 2 x Test 5	7.05008	7.02663	0.02345	0.05785	102.37223	89.00081	117.75257	Yes
Test 2 x Test 6	7.05008	7.12486	-0.07478	0.05368	92.79455	81.08940	106.18933	Yes
Test 2 x Test 7	7.05008	7.02326	0.02682	0.05450	102.71794	89.66946	117.66521	Yes
Test 3 x Test 4	7.04787	7.12940	-0.08153	0.03752	92.17081	82.34434	103.16991	Yes
Test 3 x Test 5	7.04787	7.02663	0.02124	0.06087	102.14651	88.48503	117.91722	Yes
Test 3 x Test 6	7.04787	7.12486	-0.07699	0.04698	92.58995	81.61751	105.03749	Yes
Test 3 x Test 7	7.04787	7.02326	0.02461	0.05414	102.49146	89.51164	117.35345	Yes
Test 4 x Test 5	7.12940	7.02663	0.10276	0.04973	110.82306	97.33518	126.17997	No
Test 4 x Test 6	7.12940	7.12486	0.00454	0.02663	100.45474	91.35295	110.46338	Yes
Test 4 x Test 7	7.12940	7.02326	0.10614	0.07313	111.19731	95.00445	130.15013	No
Test 5 x Test 6	7.02663	7.12486	-0.09823	0.04492	90.64426	80.12613	102.54312	Yes
Test 5 x Test 7	7.02663	7.02326	0.00337	0.09858	100.33770	83.58158	120.45304	Yes
Test 6 x Test 7	7.12486	7.02326	0.10160	0.08088	110.69394	93.80935	130.61754	No

*: Logarithmic scale **: Original scale

$D = \tilde{\delta}_h - \tilde{\delta}_{h'}$

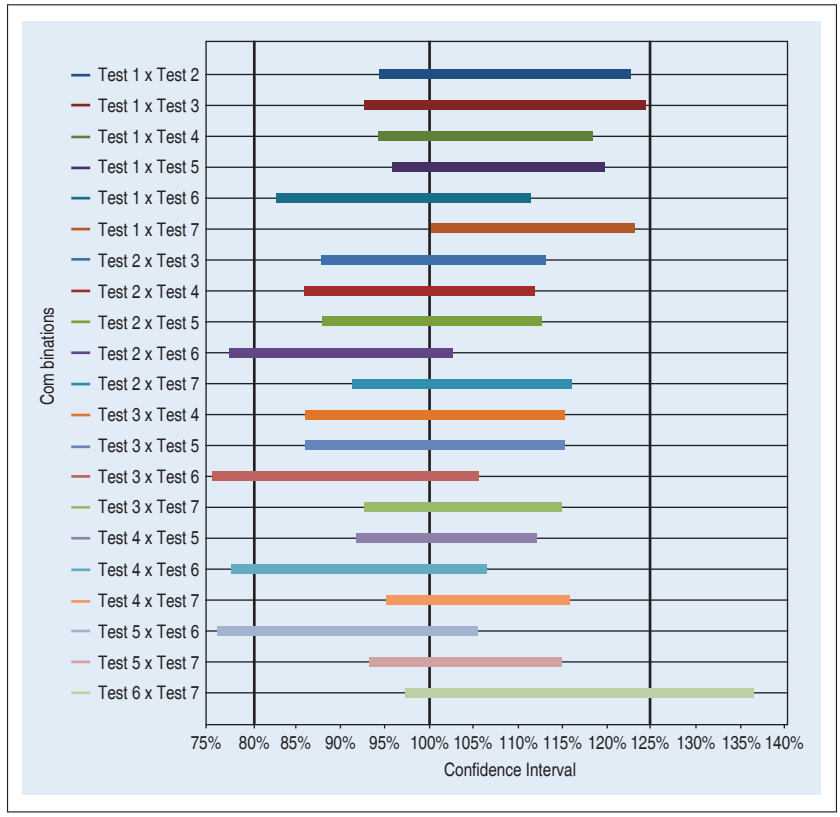

FIGURE 1: Confidence Intervals of the Binary Combinations of Test Drugs in the Meta-Analysis for C_{max}.

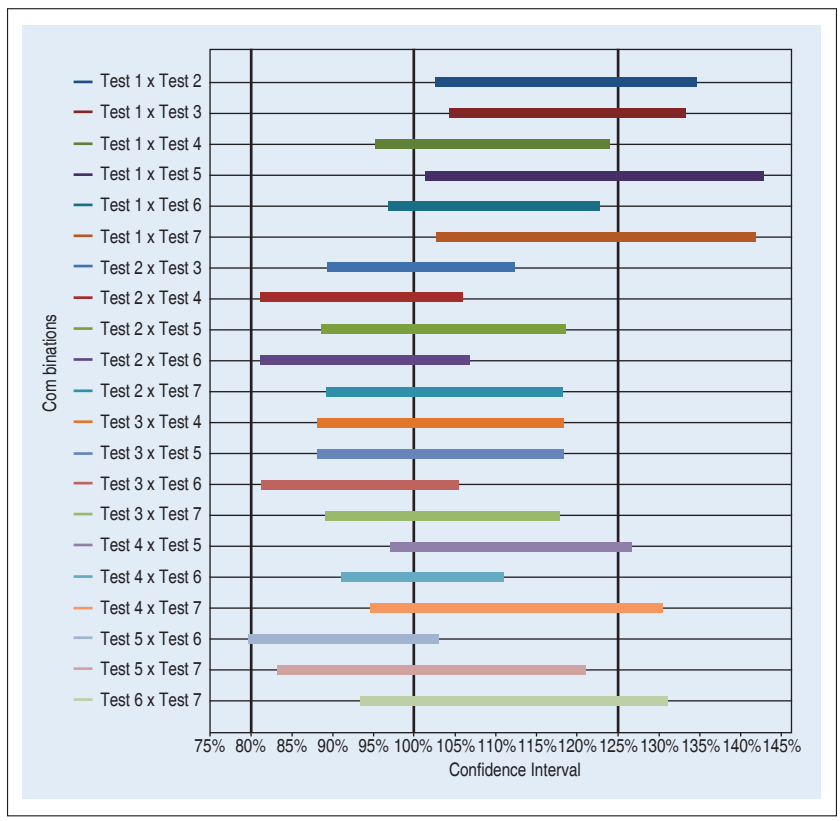

FIGURE 2: Confidence Intervals of the Binary Combinations of Test Drugs in the Meta-Analysis for $AUC_{0\text{-}tlast}$.

The meta-analysis of C_{max} has shown that the following binary combinations of test drugs were not within the bioequivalence limits of 80% to 125% (Table 1 and Figure 1): T2xT6 (78.06% to 102.07%), T3xT6 (76.15% to 105.11%), T4xT6 (78.17% to 105.97%), T5xT6 (76.64% to 104.94%) and T6xT7 (97.96% to 136.02%).

The meta-analysis of $AUC_{0\text{-tlast}}$ has shown that the following binary combinations of test drugs were not within the bioequivalence limits of 80% to 125% (Table 2 and Figure 2): T1xT2 (102.95% to 134.25%), T1xT3 (104.58% to 132.74%), T1xT5 (101.71% to 142.41%), T1xT7 (103.18% to 141.34%), T4xT5 (97.34% to 126.18%), T4xT7 (95.00% to 130.15%) and T6xT7 (93.81% to 130.62%).

DISCUSSION

When the number of brand-name drugs going off patent increases and the market share of the generic copies grows, bioequivalence among generic copies of the same brand-name drug becomes a very important public health issue. Thus, Chow and Liu have suggested a meta-analysis combining data of different studies of bioequivalence between generic and brand-name drugs. In their approach, a rather restricted and yet strong assumption is made that inter-subject (or intra-subject) variances are the same for all studies and all drug products. In this article, we used Chow and Shao's alternative method that relaxes this assumption.

Aiming at analyzing interchangeability between the generic drugs containing Naproxen active ingredient, a systematic bioequivalence review was conducted with nine studies analysed and reported by Novagenix. Seven of nine studies provided the pre-specified conditions and was included in the meta-analysis. A 90% confidence intervals for C_{max} and $AUC_{0\text{-tlast}}$ were constructed for each possible binary combination of the generic drugs to assess the interchangeability between them.

For $C_{max,}$ 5 of the 21 binary combinations (23.8%) have been concluded as non-bioequivalent. Test 6 has higher mean value for C_{max} than other generic drugs and is closer to only Test 1. Test 6 was found only interchangeable with Test 1 and not interchangeable with others. Other six drugs were considered interchangeable with each other.

For $_{AUC0\text{-tlast},}$ 7 of the 21 binary combinations (33%) have been concluded as non-bioequivalent. The mostly not interchangeable generic drugs are Test 1 and Test 7. Test 1 was not interchangeable with four of six drugs and Test 7 was not interchangeable with three of six drugs. Test 1 has the highest mean value and Test 7 has the lowest mean value for $AUC_{0\text{-tlast.}}$

The 90% confidence intervals for the ratios of both C_{max} and $AUC_{0\text{-tlast}}$ should be contained within the limits 0.80–1.25. 10 of the 21 binary combinations (47.6%) which fulfill this conditon are T1xT4, T1xT6, T2xT3, T2xT4, T2xT5, T2xT7, T3xT4, T3xT5, T3xT7 and T5xT7. It can be concluded that only these combinations are interchangeable.

Non-interchageability is particularly important for a medicine of narrow therapeutic index, whose lack of therapeutic effect or presence of toxic effects can significantly impair efficacy and safety.[7] Although Naproxen is a very safe medicine, with a wide therapeutic window, the results have suggested that the replacement of a generic drug with another can determine different therapeutic responses.

CONCLUSION

We combined independent bioequivalence studies based on the fact that they reached the same conclusion of bioequivalence compared with the same brand-name drug. When assessing the interchangeability

between generic drugs, some of the combinations may not match the acceptable range. Thus, the pharmacokinetic behaviour and therefore the efficacy of the drug product may change and switching a patient from one generic drug to another is leading to a major safety concern. The clinical importance of those findings, in regard to quality, safety and efficacy requires further investigation through clinical trials comparing the different pharmaceutical formulations of Naproxen.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Emel Doğan Kurtoğlu, Merve Gülşah Ulusoy;* ***Design:*** *Emel Doğan Kurtoğlu, Merve Gülşah Ulusoy*; ***Control/Supervision:*** *Onursal Sağlam*; ***Data Collection And/Or Processing:*** *Emel Doğan Kurtoğlu, Merve Gülşah Ulusoy;* ***Analysis And/Or Interpretation:*** *Emel Doğan Kurtoğlu, Merve Gülşah Ulusoy*; ***Literature Review:*** *Emel Doğan Kurtoğlu, Merve Gülşah Ulusoy*; ***Writing The Article:*** *Emel Doğan Kurtoğlu, Merve Gülşah Ulusoy*; ***Critical Review:*** *Onursal Sağlam*

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