ZKTB ORIGINAL RESEARCH

Amazing Supremacy of Thiopental Compared to Propofol in Rat Bronchi with Supramaximal Tonus

Supramaximal Tonuslu Rat Bronşlarında Propofol ile Karşılaştırılan Thiopental'in Şaşırtıcı Üstünlüğü

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ABSTRACT

Objective: *Bronchospasm is an undesirable phenomenon in all phases of operation and anesthesia.Tracheal intubation after induction of anesthesia causes a measurable increase in the resistance of the respiratory system, which often results in bronchoconstriction.Propofol and thiopental have been used as an intravenous anesthetic agent in induction of anesthesia for many years. Barbiturates are recommended not be used in patients with risks due to bronchospasm-causing effects. Propofol is generally recommended for patients with asthma and bronchospasm due to bronchodilatation and muscle relaxant effects. In our study, we aimed to demonstrate this superiority of propofol to thiopental in rat bronchi with supramaximal tonus in a bronchospasm model.*

Material and Methods: *A total of 30 adult male rats were divided into four groups. Double-blinded group T1 received 1x10-5 M thiopental at supramaximal contraction. In Group T2, 1x10-6M thiopental was applied at supramaximal contraction while in Group P1 1x10-1M propofol was applied at supramaximal contraction and in Group P2, 1x10-2M propofol was applied. Tissue voltages were measured with MAY GTA0303 GENIUS TRANSDUCER AMPLITUDE® and recorded in the Acknowledge MP100® program.*

Results: *In Group T1, the reduction in tonus was statistically significant (estimated mean difference, -0.41; 95% confidence interval [CI], -0.36 to 1.18; p=0.000. In Group T2, the tonus difference was statistically significant (estimated mean difference, -0.20; 95% confidence interval [CI], -0.62 to 1.03; p=0.001).There was no statistically significance between tonus levels in neither group P1 nor group P2 before and after the implementation.*

Conclusion: *In our study, relaxation effect in two different doses of thiopental was shown in rat bronchus tissue in in vitro bronchospasm model. Propofol did not show any relaxation or contraction responses in two separate doses. Surprisingly, Our results suggest that propofol has no direct bronchodilatation effect and thiopental directly provides bronchodilation. Consequently, we noticed that the effect of thiopental dose-dependent bronchodilatation is not well debate in the literature. For this reason, direct bronchodilatation doses of thiopental should be determined in further clinical and experimental studies.*

Keywords: *propofol, tiopental, isolated tissue bath, rat*

ÖZET

Amaç: *Bronkospazm, operasyonun ve anestezinin tüm aşamalarında ve istenmeyen bir fenomendir. Anestezi indüksiyonu sonrası trakeal entübasyon, sıklıkla bronkokonstriksiyona neden olan solunum sisteminin direncinde ölçülebilir bir artışa neden olur. Propofol ve tiyopental uzun yıllardan beri anestezi indüksiyonunda intravenöz anestezik ajan olarak kullanılmaktadır. Barbitüratlar, bronkospazmaya neden olan etkilerinden dolayı riskli hastalarda kullanılması tavsiye edilmez. Bronkodilatasyon ve kas gevşetici etkisi nedeniyle astım ve bronkospazm riski olan hastalarda genellikle propofol önerilir. Bu çalışmada, rat bronşlarında supramaksimal tonus oluşturulmuş bronkospazm modelinde propofolun thiopentale olan bu üstünlüğünü göstermeyi amaçladık.*

Gereç ve Yöntemler: *Toplam 30 erişkin erkek sıçan dört gruba ayrıldı. Çift-kör grup T1 supramaximal kontraksiyonda 1x10-5 M tiyopental aldı. Grup T2'de supramaksimal kontraksiyonda 1x10-6M tiyopental, supramaksimal kontraksiyonda Grup P1 1x10-1M propofol ve Grup P2'de 1x10-2M propofol uygulandı. Doku voltajları MAY GTA0303 GENIUS TRANSDUCER AMPLITUDE® ile ölçüldü ve Acqunowledge MP100® programına kaydedildi.*

Bulgular: *Grup T1'de tonustaki azalma istatistiksel olarak anlamlı bulundu (tahmini ortalama fark, -0.41;% 95 güven aralığı [CI], -0.36 ile 1.18; p = 0.000. T2 grubunda tonus farkı istatistiksel olarak anlamlıydı (tahmini). ortalama fark, -0.20;% 95 güven aralığı [CI], -0.62 ile 1.03; p = 0.001). Uygulama öncesi ve sonrası P1 grubu ve grup P2'de tonus seviyeleri arasında istatistiksel olarak anlamlı bir fark bulunmadı.*

Sonuç: *Çalışmamızda in vitro bronkospazm modelinde rat bronş dokusunda iki farklı tiyopental dozunda gevşeme etkisi gösterilmiştir. Propofolün iki ayrı dozunda ise herhangi bir gevşeme veya kasılma yanıtı saptanmamıştır. Şaşırtıcı olarak, bu çalışma propofolun doğrudan bronkodilatör etkisinin olmadığını ve tiyopentalin direkt olarak bronkodilatasyon sağladığını göstermektedir. Sonuç olarak, tiyopental doza bağımlı bronkodilatasyonun etkisinin literatürde iyi tartışma olmadığını fark ettik. Bu nedenle daha ileri klinik ve deneysel çalışmalarda tiyopental direkt bronkodilatasyon dozları belirlenmelidir.*

Anahtar Kelimeler: *propofol, thiopental, izole doku banyosu, rat*

INTRODUCTION

Per and postoperative respiratory complications are the most common and important events that increase anesthesia and surgical risk (1-5). Inparticular, bronchospasm is an undesirable phenomenon in all phases of operation and anesthesia. Tracheal intubation after induction of anesthesia causes a measurable increase in the resistance of the respiratory system, which often results in bronchoconstriction (6). Propofol and thiopental have been used for many years as an intravenous anesthetic agent in induction of anesthesia (7). Thiopental has been extensively studied correlation between intraoperative bronchospasm (8). This effect of thiopental is believed that is result of cholinergic stimulation (9). It is also recommended that barbiturates not be used in patients at risk due to bronchospasm-causing effects. Propofol also is generally recommended for patients with asthma and bronchospasm due to bronchodilatation and muscle relaxant effects. Although many anaphylactic allergic reactions and bronchospasm have been reported related with propofol, metaanalyses and reviews report more reliable propofol than thiopental in patients with asthma and risky bronchospasm. Many studies have shown that propofol is a beter option than barbiturates in terms of risk of bronchoconstriction (10). In our study, we aimed to demonstrate this superiority of propofol to tiopental in rat bronchi with supramaximal tonus in a bronchospasm model.

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MATERIAL AND METHOD

Animals

4-6 month old 30 male rats (350-400g) were obtained from Experimental Animal Center of Adnan Menderes University (ADU) and all experiments were performed in accordance with the principles and guidelines of ADU Animal Ethical Committee's approval (HADYEK 64583101/2016/064)

Experimental design

Krebs-Henseleit solution contains (g/L): glucose 2, $MgSO_4$ 0.41, KPO_4 0.16, KCl 0.35, NaCl 6.9, CaCl 0.373, $NaHC0_3$ 2.1 (ph: 7.4) in isolated tissue bath. The buffer solution was oxygenated with 95% O_2 and 5% CO_2. During the equilibrium period in the organ bath, the Krebs solutions of the organs were washed 4 times in one hour (once a 15-minute-period) during the equilibrium period, 1 g basal tension was slowly supplied.

All rats were anesthetized with 50mg/kg ketamine. While heart beat was continued after the anesthesia, trachea was removed with thoracotomy and sternotomy in 3mm-rings and suspended with 1g rest tension in 10 ml organ bath.

After the left main bronchus of rats were removed, all rats were decapitated and sacrificed. Isometric contractions of circular smooth muscles were measured with MAY FDT 10-A ® transducer. After the viability of the tissues was demonstrated with acetylcholine and atropine, the washed tissues were waited to reach the basal tonus.

Because viability of the bronchus could not be shown, 6 rats were excluded from the study. Ach was then administered to create supramaximal contractions. Twenty-four rats that provided least 7% increase and at least 15 minutes plateau were included the study and were separated to 4 groups using a random number table. As double-blinded group T1 received 10-5 M thiopental at supramaximal contraction, Group T2 applied 10-6M thiopental at supramaximal contraction, Group P1 applied 10-1M propofol at supramaximal contraction, Group P2 applied 0.05mM propofol one. Tissue voltages were measured with MAY GTA0303 GENIUS TRANSDUCER AMPLITUDE® and recorded in the Acknowledge MP100® program.

Data presentation and statistics

The homogeneity test of tonus levels both before and after implementation of all groups of thiopental and propofol was performed. None of them did not show a normal dispersion which were determined. Comparisons of groups pre and post-performing were made using the nonparametric Wilcoxin test and Paired sample t test in the Spss 22.0 program and $p < 0.05$ was considered statistically significant..

RESULTS

In the 1mmol group of thiopental, it were determined level of supramaximal tonus was at 0.40 ± 0.9 before implementation which decreased to level of 0,20 ± 0,9 after implementation. The reduction in tonus was statistically significant (estimated mean difference, -0.41; 95% confidence interval [CI], -0,36 to 1,18; P = 0.000), (Figure 1).

However, in 0,1mmol group of thiopental, level of supramaximal tonus was at 0.20 ± 1.0 before implementation which decreased to level of 0,10 ± 0,94 after implementation that were determined. The difference was statistically significant (estimated mean difference, -0,20; 95% confidence interval [CI], -0.62 to 1,03; P = 0.001) (Figure 1).

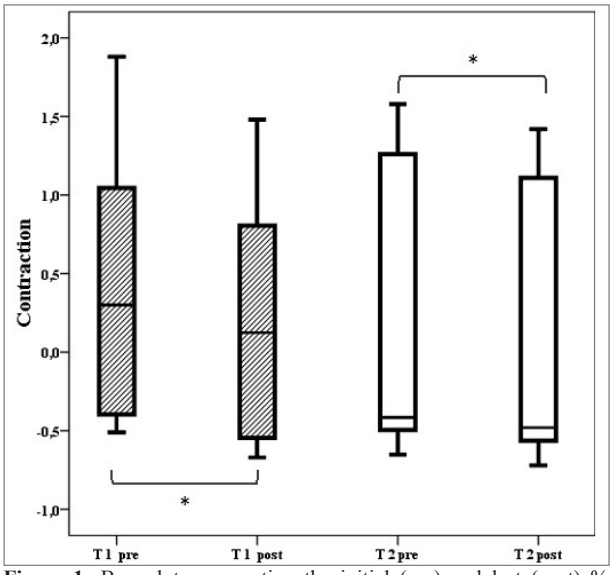

Figure 1: Box plot representing the initial (pre) and last (post) % contractions of bronchiols after diffrent doses of tiopental. Ends of the whiskers represent the 10th and the 90th percentiles. Horizontal lines represent mean values. *= p<0,001 Paired sample t-test results.

But, there was no statistically significant difference between tonus levels in neither propofol 20 mmol nor 2 mmol groups before and after the implementation (in propofol 20 mmol group, tonus before implementation was at 0,20 ± 0,9, tonus after implementation was at 0,20 ± 0,9 estimated mean difference, 1,80; 95% confidence interval [CI], 0.05 to 0.09; P = 0,476, in propofol 2mmol group, tonus before implementation was at 0,20 ± 0,9, tonus after implementation was at 0,20 ± 0,9 estimated mean difference 0.16; 95% confidence interval [CI], -0.01 to -0.01; P = 0,720) (Figure 2).

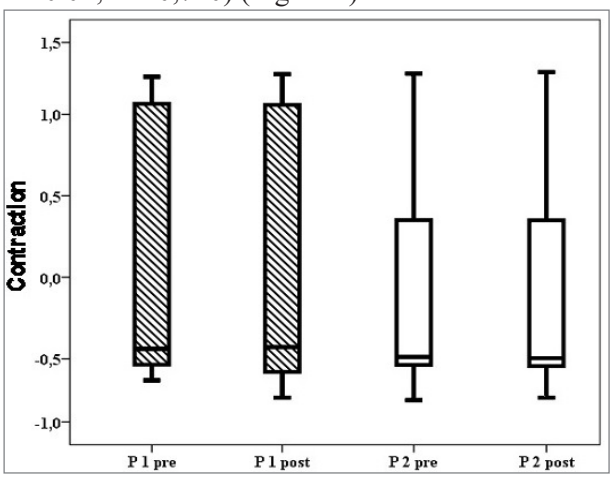

Figure 2: Box plot representing the initial (pre) and last (post) % contractions of bronchiols after diffrent doses of Propofol. Ends of the whiskers represent the 10th and the 90th percentiles. Horizontal lines represent mean values. No statics were found Paired sample t-test results.

The effect of thiopental and propofol on bronchial tonus with supramaximal contraction in a rats is seen in figure 3.

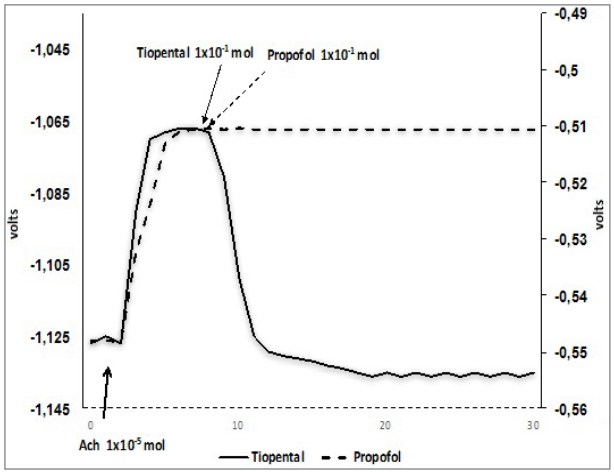

Figure 3: Effects of Tiopental and Propofol on supramaximal tonus. Straight line denotes the contraction (%) changes on Tiopental (1x10-1 mol). Dotted line denotes the contraction (%) changes on Propofol (1x10-1 mol).

DISCUSSION

In our study, relaxation effect of two different doses of thiopental was shown in rat bronchus tissue with in vitro bronchospasm model. Propofol has not received any relaxation or contraction responses in two separate doses.

These results do not support the data in many studies comparing thiopental and propofol. If we examine it chronologically; Firstly, Regarding thiopental, in 1943, Adriani and Rovenstine showed sodium thiopental caused bronchospasm in dogs and rats (11). When we arrived in 1968, Fletcher et al. showed relaxation on the trachea (12). In the following years, Edney and Downes reported that barbiturates had no effect on smooth muscle (13). Lenox et al. have found contraction at 10-6-10-3M doses relaxation and at 10-3-3x10-3M doses as dose-related for thiopental in a study in guinea pig trachea (14). They have shown the effect of relaxation as same as our study. However we have found relaxation even in doses of their contractions. Reason of the difference we depended on that we studied in the bronchial tissue while they studied in the tracheal tissue. Mustafa T et al. a study in sheep found that thiopental caused tracheal constriction by histamine release from mast cells but led to dilatation in small airways and small intralobular bronchi and did not show a clear change in airway resistance with thiopental (15). Their study explains the reason of these different findings between our study and Lenox et al. Hirota K et al. (9) thiopental has reported that induces bronchospasm by direct, cholinergic stimulation and histamine release and not so thoroughly described of bronchoconstriction mechanisms.

They have detected the bronchoconstriction effect of thiopental via muscarinic receptors at the end of their studies. Interestingly, they have observed that bronchospasm was prevented in the atropine-added thiopental group (16).

It has also been reported that dogs with bronchoconstriction with thiopental increase tone by 10-20% and these effects are mediated by muscarinic and 5HT receptors (17).

Secondly, Regarding propofol, There are numerous publications on propofol's bronchodilatation effect in asthmatic patients (18-20). Several studies have shown that its bronchodilatation effect is due to antiinflammatory effects in neutrophil-mediated responses (21-23). In experimental models it has been reported that propofol effectively inhibits allergic airway inflammation by inhibiting NF-kB activation in vitro and in vivo and thus may be used in the treatment of allergic asthma (24). Many studies also remarks that propofol induces bronchodilatation by weakening smooth muscle contraction in both healthy and asthmatic patients. However, we found that the propofol bronchospasm model was ineffective in rats. The reason for this is that in the light of publications,we think it is based on other pathways mechanism of bronchodilatation of propofol in stead of direct muscarinik or colinergic effect.

Although the reviews related anesthesia management of patients with asthma or COPD have shown more superiority propofol than thiopental, we found opposite. When we try to explain of thiopental's bronchodilatation effect and propofol's uneffecting on bronchoconstruction model, in fact that we can claim that thiopental provides bronchoconstruction or relaxation as asssociated with dose and, propofol has no direct bronchodilatation effect on cholinergic or muscorinic reseptors.

Consequently, our study showed on bronchospasm that thiopental inhibits bronchoconstriction at some doses and propofol has no direct bronchodilatation effect on cholinergic or muscarinic receptors.

Thiopental's dose-dependent bronchodilatation effect should not be forgotten, even if long-term research and clinical experiences recommends propofol for patients with asthma and bronchospasm risky in anesthesia management principles. For this reason, bronchodilatation doses of thiopental should be determined in further clinical and experimental studies.

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