

Theophylline impact on weaning in oxygen-dependent infant followed in an outpatient Kangaroo Program

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May 4, 2023

Abstract

Background: Theophylline was an orally administered xanthine used for the treatment of apnea of prematurity and Bronchopulmonary Dysplasia in the ambulatory follow-up of Low-Birth-Weight infants (LBWI) with oxygen-dependency in the Kangaroo Mother Care Program (KMCP). Theophylline's main metabolic product is caffeine; therefore, it was an alternative due to the frequent lack of ambulatory oral caffeine in low and middle-income countries. *Purpose:* to assess the effectiveness of oral Theophylline in decreasing days with oxygen and to describe frequency of adverse related events. *Method:* quasi-experiment before and after withdrawal of Theophylline given systematically to LBWI with ambulatory oxygen in two KMCPs. *Results:* 729 patients were recruited; 319 with Theophylline and 410 after Theophylline withdrawn. The Theophylline cohort had less gestational age, less weight at birth, more days in Neonatal Intensive Care Unit, more days of oxygen-dependency at KMCP admission, and more frequencies of Intrauterine Growth Restriction and apneas. After adjusting with propensity score matching, multiple linear regression was done, and analysis showed that nutrition had a greater effect on days of oxygen-dependency than the fact of receiving Theophylline. No differences were found in readmissions up to 40 weeks, nor in the frequency of intraventricular hemorrhage or neurodevelopmental problems. The Theophylline group had more tachycardia episodes. *Conclusions:* we did not find evidence of oral Theophylline effect on the reduction of days of oxygen-dependency. For the current management of oxygen-dependency in newborns, the importance of KMCPs nutritional protocols based on exclusive breast feeding whenever possible, is the challenge for these fragile infants.

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Short title: Theophylline impact in oxygen-dependent infant

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Word count of the manuscript body: 3023 words.

Acknowledgments

The authors thank Drs Andrea Conde, Johana Forero, and Claudia Giraldo, Pediatric residents at the Javeriana University, for their collaboration in data collection and Dr. María Calume, who collaborated in coordinating the study, and to the nurses from the KMCP who helped in the study development.

Declarations

Funding Statement: This project was supported by the Kangaroo Foundation and the Integral Kangaroo Mother Care Program in Bogotá, Colombia.

Financial Disclosure : The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Availability of data and material: on request from the authors.

Code availability: Not applicable.

Authors' Contributions:

- Dr. Montealegre was responsible for generating research protocol, processing of the database, overseeing all data collection, analysis, writing and revising the manuscript.
- Dr Charpak was responsible for processing of the database, analysis, writing and revising the manuscript.
- Dr Lince was responsible for writing and revising the manuscript.

The three authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethics approval: this study was conducted in agreement with the principles established in the Declaration of Helsinki and with the standards of Good Clinical Practice of the country. The ethics and research committee of the Kangaroo Foundation approved the protocol.

Consent for publication: The authors certify the accuracy of content given to the journal, in particular, the names of coauthors present and correctly spelt, and that addresses, and affiliations are up to date. The corresponding author ensures that the co-author have agreed to all of the contents and will notify to the co-author when the manuscript is accepted. The corresponding author is answerable to all the inquiries on behalf of the co-author. The corresponding author ensures that both authors have seen and approved the final version of the paper and are aware of the submission of the paper. The corresponding author is solely responsible for maintaining a proper communication with the journal and with co-author, before and after publication.

Abstract (249/250)

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withdrawal of Theophylline given systematically to LBWI with ambulatory oxygen in two KMCPs. *Results:* 729 patients were recruited; 319 with Theophylline and 410 after Theophylline withdrawn. The Theophylline cohort had less gestational age, less weight at birth, more days in Neonatal Intensive Care Unit, more days of oxygen-dependency at KMCP admission, and more frequencies of Intrauterine Growth Restriction and apneas. After adjusting with propensity score matching, multiple linear regression was done, and analysis showed that nutrition had a greater effect on days of oxygen-dependency than the fact of receiving Theophylline. No differences were found in readmissions up to 40 weeks, nor in the frequency of intraventricular hemorrhage or neurodevelopmental problems. The Theophylline group had more tachycardia episodes. *Conclusions:* we did not find evidence of oral Theophylline effect on the reduction of days of oxygen-dependency. For the current management of oxygen-dependency in newborns, the importance of KMCPs nutritional protocols based on exclusive breast feeding whenever possible, is the challenge for these fragile infants.

Keywords: Theophylline; Infant, Low Birth Weight; Kangaroo-Mother Care Method; Therapy, Oxygen Inhalation.

What is known:

Theophylline was an alternative for the ambulatory management of oxygen dependent preterm infants in face of the lack of availability of oral caffeine.

What is new:

- In this quasi-experiment before and after withdrawal of Theophylline given systematically to all LBW infants with ambulatory oxygen, there was no evidence of Theophylline effect on decreasing days of oxygen dependence.
- Infants in Theophylline group had more tachycardia episodes.
- In the multivariate analysis, daily weight gain and exclusive breast feeding had important effect on reducing days of oxygen dependency.

List of abbreviations in alphabetical order

BPD: Bronchopulmonary Dysplasia

CA: Corrected Age

EBF: Exclusive Breast Feeding

GA: Gestational Age

IQR: Interquartile range

IUGR: Intrauterine Growth Restriction

IVH: Intraventricular Hemorrhage

KF: Kangaroo Foundation

KMCP: Kangaroo Mother Care Program

LBWI: Low Birth Weight Infants

OD: Oxygen-Dependent

ROP: Retinopathy of Prematurity

SD: Standard Deviation

Introduction

According to the Kangaroo Foundation (KF) database, 11,953 oxygen-dependent (OD) low birth weight infants (LBWI) were followed in the ambulatory Kangaroo Mother Care Program (KMCP) in Bogotá, Colombia between 1998 and the first semester of 2021. It was observed that the frequency of oxygen dependency

decreased from 43% between 2003 and 2007 to 7% between 2018 and 2021. Patients <32 weeks gestational age (GA) were between 41-62%. In addition, hospital stay was variable according to the severity of perinatal compromise.

For the last 24 years, the KMCP has managed LBWI with ambulatory oxygen. A first study conducted in 2004 in 12 hospitals of Bogotá, showed that weight, GA at birth, mechanical ventilation, intrauterine growth restriction, and type of institution (i.e., low vs. intermediate-high mortality) were independently associated with bronchopulmonary dysplasia (BPD) of increasing severity or even death¹. Of this cohort, 194 patients were followed up to 1-year corrected age (CA); breastfeeding at term was successful in 76%, growth at one year was appropriate, 74% of the cohort were still receiving home oxygen at 40 weeks and at 3 months 23%. Moreover, around 57 % of the cohort were readmitted to hospital at least once, 47% of them because of respiratory conditions². A latter study was conducted between 2017 and 2018 with 445 patients [?]33 weeks GA and OD at admission. It was observed that 56% had a history of sepsis and 49% had received invasive ventilation. Multivariate analysis also found that oxygen dependency was associated with low hemoglobin levels at admission, the number of blood transfusions received, and lower GA. On the other hand, weight gain and exclusive breastfeeding until oxygen weaning were identified as protective factors³.

Different therapeutic approaches have been described to prevent and treat BPD, such as xanthines, diuretics, bronchodilators, vitamin A and D, corticosteroids, and probiotics, without achieving clear effectiveness^{4,5}. For more than 40 years, xanthines have been used to manage premature patients⁶. Within this group Caffeine, Aminophylline, Doxapram, and Theophylline stand out, with the first one being the most well-known. These medications work by stimulating respiratory centers and promoting diaphragmatic contractility, improving pulmonary distensibility, and reducing airway resistance. These effects are of particular importance in apnea of prematurity and in chronically ventilated newborns who may develop muscular fatigue with skeletal and diaphragmatic muscular atrophy. By improving muscle contractility, they contribute to chest wall stabilization, increasing functional residual capacity and allowing successful extubation; this last fact has been associated with less days with oxygen^{7,8}.

Theophylline is an orally administered xanthine used for the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease⁹. It is extensively metabolized, and its main metabolic product is caffeine due to N-methylation. Apnea of prematurity and BPD treatment has been described as its principal uses¹⁰. Theophylline (1,3-dimethylxanthine) therapy in newborns has the inconvenience of greater toxicity due to its erratic absorption and elimination, with a prolonged half-life of approximately 30 hours, nine times longer than in adults, due to the immaturity of the cytochrome monooxygenase P450 enzymes¹¹. Several adverse effects associated with Theophylline use have been described, such as cardiac arrhythmias, nausea, vomiting, headache, diarrhea, irritability, and insomnia^{12,13}, without having a specific antidote.

From 1996 until 2017 oral Theophylline was systematically implemented in ambulatory KMCPs in Colombia as an adjuvant medication to reduce the number of days of ambulatory oxygen¹⁴. In 2017, in view of the available evidence of increased risk of toxicity with Theophylline, routine treatment was discontinued, and recommendations were modified in the new KMC technical guidelines of the Health Ministry¹⁵.

This study aims to evaluate the effectiveness of oral Theophylline to reduce the days of oxygen dependency and to assess the frequency of adverse events related to this drug.

Materials and Methods

Quasi-experiment before and after withdrawal of systematic Theophylline given to LBWI with ambulatory oxygen in two KMCPs. We compared two cohorts of LBWI OD at admission in the outpatient KMCPs of two teaching hospitals in Bogotá, Colombia (Hospital Universitario San Ignacio and Hospital Infantil San José).

The first cohort received oral Theophylline up to 40 weeks' GA between July 25, 2017 and May 31, 2018. The second cohort included OD LBWI admitted to the KMCP without Theophylline treatment, between June 01, 2018 and April 20, 2019. Patients with a history of seizures, congenital heart disease or cardiac

arrhythmia were excluded.

We compared days of oxygen requirement, hospital readmissions, number of KMCP consultations, feeding pattern, anthropometric measures, incidence of tachycardia, gastroesophageal reflux (GER), colic, seizures and other side effects that could be attributed to oral Theophylline treatment at 40 weeks GA and at oxygen weaning.

Sample size

It was calculated using the software STATA 14. The main outcome was days of oxygen dependency during follow-up in the ambulatory KMCPs. According to the KMCP database, OD patients received on average 70 days of oxygen (SD 64 days). To obtain a 15 days reduction in oxygen requirement, an alpha of 0.05 and a power of 80% with two-tailed estimation, and follow-up losses of 20%, the sample size per group was 344 patients.

Intervention

- In the first cohort, LBWI OD infants at entry received oral Theophylline (Teolixir®) 4 mg/kg/day dose up to 40 weeks, divided into three doses and multivitamins. With the new evidence and Kangaroo Guidelines update published at the end of 2017, Theophylline use was suspended for the second cohort. There was a progressive transition over a 4-month period.
- All infants received the same outpatient Kangaroo Protocol interventions consisting of a close, multi-disciplinary follow-up until oxygen weaning as mentioned below:
- Kangaroo position (KP): newborn in skin-to-skin contact, 24 hours a day, placed in a firm upright position, between mother's breasts, and under mother's clothes. Mothers not only regulate infants' body temperature, but also are the main sources of nourishment and stimulation. An elastic support is used, allowing the KP provider to relax and sleep while the infant remains permanently in KP. The elastic support also helps to prevent the infant's airway from being obstructed by position changes, particularly important due to the hypotonia usually present in premature infants, which can lead to postural obstructive apneas.
- The baby can be fed at any time, without leaving the KP. Another person (e.g., the father) can replace KP with the mother. The caregiver should sleep in a semi-reclined posture to avoid gastroesophageal reflux.
- The KP is maintained until the infant shows clear signs of intolerance or discomfort (e.g., sweating, scratching, screaming)¹⁶.
- Exclusive breastfeeding (EBF) is introduced whenever possible and is initially given on a very strict schedule (i.e., every 2 hours). The weight gain is aimed to be at least the same as that of intrauterine development (15-20 g/kg/day). If this goal is not achieved with exclusive breastfeeding after an intensive intervention called the ambulatory kangaroo adaptation, and after ruling out other medical conditions (e.g., anemia, infection, hypothermia, etc.), supplementation with LBWI formula is administered with a dropper or spoon to avoid interference with lactation. The supplement is calculated based on 30% of the recommended daily caloric intake. After at least one week of adequate growth, a progressive decrease in supplementation is attempted, to reach 40 weeks GA with exclusive breastfeeding.
- After discharge, patients were controlled daily, until they reached daily weight gain of 15-20 g/kg/day. Afterwards, weekly controls were performed, until term (40 weeks GA). This is an equivalent of minimal in-hospital care and could be called "minimal ambulatory neonatal care".
- Dynamic oximetry with a pulse oximeter was performed upon patients' admission. The target was to achieve oxygen saturation between 90-94% with adequate heart rate frequency while resting, sucking, and sleeping with adequate growth. Dynamic oximetry was performed weekly until oxygen weaning according to KMC protocol³.

- At admission, parents were fully educated about oxygen management at home and provided with an instructional flier.
- Follow-up program includes ophthalmologic screening and early detection of neurological conditions, with an ultrasound brain sonography.
- Anthropometric measures were carefully collected and evaluated with the Fenton-2013 charts¹⁷.

Statistical Analysis

For the analysis Stata 14 was used. Quantitative data was reported as medians with their interquartile range given their non-normal distribution. Qualitative data was reported as absolute and relative frequencies. Bivariate analysis of quantitative data was done with the Mann Whitney nonparametric test and for qualitative data we used Chi-square or Fisher's exact test.

Propensity Score Matching was done for unbalanced baseline variables between the groups. Then, multivariate analysis was performed with multiple linear regression having as dependent variable days of oxygen dependence, and as independent variables those that according to the evidence, are associated with oxygen dependence.

Results

A total of 729 patients were recruited: 319 in the Theophylline group and 410 in the non-Theophylline group.

Tables 1 and 2 summarize the two groups' baseline characteristics. No differences were found in sociodemographic variables, but significant clinical differences were identified, being infants in Theophylline group more fragile (less GA at birth and at KMCP entry, less weight at birth and at entry, more hospital stay, and less non-invasive ventilation).

Table 3 describes the follow-up results. The Theophylline group had more BPD defined as OD >28 days and GA [?] 36 weeks, but when BPD was defined as OD >28 days and GA [?]40 weeks, there was no difference between groups¹⁸. Infants who received Theophylline had a higher frequency of apneas during the hospital stay and ambulatory follow-up. Additionally, chronological age at oxygen weaning and weight at 40 weeks were higher than in the non-Theophylline group. Although the feeding pattern at oxygen weaning was similar between the two groups, the non-Theophylline group had a higher proportion of exclusive breast milk (EBM) at 40 weeks (46 vs 36%).

No differences were found in the number of readmissions up to 40 weeks. Neither in the frequency of intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) or neurodevelopmental problems.

Regarding the possible side effects associated with Theophylline treatment, we found no differences in GER or gastrointestinal disorders. However, more tachycardia episodes were recorded in the Theophylline group (1.3% vs 0).

Finally, patients in the Theophylline group had a higher percentage of losses (3.5% vs 1%), although in general, these were minor for the two cohorts.

In order to adjust for baseline differences between groups (GA, birth weight, GA at study recruitment, frequencies of IUGR and apnea, days in NICU and days with oxygen at study recruitment), we performed propensity score matching. Then, multiple linear regression with total days of oxygen dependency as the outcome variable and having received Theophylline as the exposure variable. The control variables were frequency of EBF at O2 weaning, days of mechanical ventilation, weight at study recruitment, weight gain between study recruitment and oxygen weaning and weight reached at oxygen weaning. Probable interactions were entered, and model diagnostics were performed (after individual evaluation, 6 outliers were excluded).

Tables 4 and 5 show the propensity score matching and multiple linear regression analysis. After adjusting for baseline differences between groups with propensity score matching, it was found that controlling for days of mechanical ventilation, weight at study recruitment and weight gain to reach the oxygen weaning weight (Figure 1), EBF could reduce oxygen dependency in 9 days; on the other hand, for each day with mechanical ventilation, oxygen dependency increases in 2 days. No effect of Theophylline administration was found between the two groups (682 observations, R^2 0.63, 95% CI (-1.01, 4.66) $p=0.21$).

Discussion

As the leading cause of oxygen dependency, BPD, has presented important changes in its clinical presentation and definition compared to the first study performed in 1967 by Northway¹⁹ or with the study conducted by Kangaroo Foundation in 2004 in Bogota¹. With neonatal care advances, patients nowadays are more immature but with less lung injury, and oxygen dependency is associated with restriction of alveolar septation due to antenatal infections among other causes²⁰. Currently, most units define BPD as OD >28 days and/or [?] 36 weeks GA or even OD/ respiratory support [?]40 weeks, according to GA at birth^{21–24}.

Since 1937 Theophylline therapy has been employed in patients with different respiratory diseases, mainly inflammatory processes such as bronchial asthma or chronic obstructive pulmonary disease⁹. In newborns, especially premature infants, it has been used to manage apnea of prematurity and prevent BPD, given its diuretic and anti-inflammatory properties and its effect on diaphragmatic contractility. Because of N-methylation, Theophylline is metabolized to caffeine¹⁰, and can be available in oral presentation for outpatient treatment. It became a good alternative for KMCPs managing LBWI with ambulatory oxygen, therefore its use became part of the routine management for this population¹⁴.

Over the years, toxicity concerns were found with Theophylline administration in animal models and some human case reports. Research in mice revealed that Theophylline-exposed groups presented a higher risk of involuntary movements, tachyarrhythmias, ischemic changes with ST-segment depression and increased risk of gastric ulcers²⁵. In humans, Theophylline overdose has been associated with probable status epilepticus induction and a potential mortality of 10%¹¹.

On the other hand, treatment with caffeine has shown short- and long-term effectiveness, with a lower risk of toxicity than Theophylline. Although its primary objective has been the management of apnea of prematurity, since 2006, a possible association with a decrease in BPD was described, as well as a decrease in death or disability at 18 to 21 months. These findings are probably associated with a decrease in days of mechanical invasive ventilation and by the anti-inflammatory and/or diuretic effects of xanthines⁵. Early initiation of caffeine (<2 days of life) showed a reduction in mortality and BPD incidence²⁶. A 2020 systematic review, including studies with a total of 63,315 newborns, found evidence of non-inferiority in the effectiveness of caffeine compared to the other methylxanthines for treating apneas with lower tachycardia range and complications, especially when administered early and at low doses²⁷. Other caffeine benefits are the once-daily administration and wide therapeutic range with reduced need for serum level monitoring²⁸. Given these advantages, caffeine is the xanthine of choice in newborns.

The increasing evidence of safer management with caffeine makes Theophylline a secondary option. However, in ambulatory KMCPs in low or middle-income countries it remained in use, due to the lack of ambulatory oral caffeine. Evidence from recent years has indicated that the use of xanthines in premature infants is limited to treatment of apnea of prematurity, without finding a clear benefit in the reduction of days of oxygen dependency or long-term effects⁶. We performed this study to obtain more evidence on this statement, given the controversy of the benefit of xanthines in reducing oxygen dependency. When adjusting for aspects related to better care over time, such as ventilatory support practices and nutrition variables, we did not find any effect of Theophylline in reducing days of OD; on the other hand, EBF and weight gain were significative.

These results support the decision to discontinue the systematic use of this medication in our ambulatory

program and the importance of nutrition based on EBF and monitored with weight gain. For several years, emphasis has been placed on nutrition as a crucial factor for lung growth and repair²⁹. Researchers suggest that these patients should receive a total daily intake between 135 to 150 cc/kg/day with a caloric supply between 120 to 150 kcal/kg/day, meaning high energy intake and small volumes³⁰. Other studies have also found that patients who were breastfed (with or without fortification) had a reduction in the frequency of BPD. In a systematic review by Villamor et al. with a total of 15 studies (4984 patients and 1416 cases of BPD), it was found that EBF was associated with a significant reduction in the risk of BPD adjusting for gestational age in the meta-regression (RR 0.74, 95%CI 0.57-0.96, 5 studies). The authors argue that this is related to the known presence of bioactive nutritional components in breast milk that counteract factors such as oxidative stress, inflammation and nutritional deficiencies involved in the pathogenesis of BPD. Additionally, indirectly, the effect of breastfeeding on reducing the incidence of necrotizing enterocolitis and late sepsis may contribute to a lower frequency of this entity³¹. In our study, a high percentage of patients in both cohorts received EBF or formula+ breastfeeding at weaning (89%), probably because of the KMC benefits on breastfeeding^{32,33}, but only those with EBF had the advantage of less days with oxygen as in Villamor's study.

We found no significant differences between groups in the frequency of BPD at 40 weeks, ROP, IVH, neurological abnormalities and re-hospitalizations up to 40 weeks.

Regarding side effects, there were no differences in gastrointestinal or neurological problems associated with Theophylline. However, as reported in the literature, there was a greater number of tachycardia episodes^{12,34}.

In the multivariate analysis, it seems that weight at ambulatory KMCPs admission, weight gain during ambulatory follow-up and EBF have a greater factor effect on days of oxygen dependency than the fact of receiving or not Theophylline. This results could be related to the already known nutritional impact on BPD^{31,35,36}. In fact, we found a similar association between weight at weaning and days of oxygen dependence in another recent analysis published in 2021³. This multivariate analysis explained 63% of the variance of days of oxygen dependency for our population.

Given these results we hypothesize that EBF enhanced with KMC, increases pulmonary tissue repair, nutritional recovery and growth, with the consequent effect on the reduction of days with oxygen.

Numerous newborn units are now being opened in low- and middle-income countries, increasing the survival of the most immature LBW infants but with very aggressive management. Goals of non-aggressive ventilation, nutrition with breast milk as early as possible, humanization and early discharge to ambulatory KMCPs should be part of the management of these units to allow survival with quality and reduced morbidity such as that caused by oxygen dependency. Current evidence shows that pharmacological therapies have no significant effect in oxygen dependence treatment³⁷.

The main limitation of this study was the effect of improvement in perinatal care during the two periods of assessment, which generated the baseline difference between the two groups. We controlled for this effect of time by applying propensity score matching and multivariate analysis, which allowed us to hypothesize possible associations on days of supplementary oxygen.

In conclusion, we did not find evidence of an effect of oral Theophylline on the reduction of days of oxygen dependency for LBWI managed with ambulatory oxygen. On the contrary, there was a higher frequency of tachycardia. For the current management of oxygen dependency in the newborn, the importance of optimal nutrition, including EBF that allows adequate weight gain with pulmonary tissue repair, is a challenge.

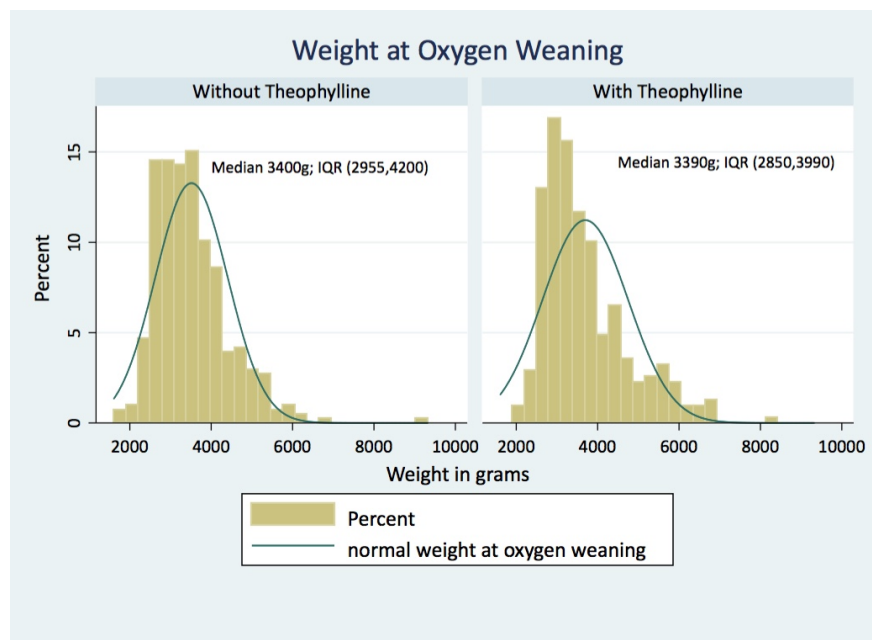
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