The Cardiac Side Effects of Levalbuterol versus Albuterol in Pediatric Patients Presenting with Acute Asthma Attacks: A Systematic Review and Meta-Analysis

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Abstract

Aims: Beta-2 agonists are the standard of care for asthmatic patients. Racemic albuterol and levalbuterol are two of the most commonly used bronchodilators of this category. Although their efficacy has been tested excessively, their effects on heart rate remain debatable by many conflicting articles in the medical literature. This review aims to summarize all available data in the literature concerning the effects of Racemic Albuterol versus Levalbuterol on heart rate in asthmatic children. Methods and Results: Our search covered five different databases: PubMed, SCOPUS, Wiley Online Library, Web of Science, and Cochrane Library. We included clinical trials investigating heart rate in asthmatic pediatric patients; either as a primary or secondary outcome. The primary outcome was heart rate changes. Secondary outcomes were respiratory rate, FEV1 peak percent changes, potassium serum levels, SpO2 peak changes, asthma score, and adverse effects. Eight clinical trials were included; seven of them were eligible for meta-analysis. In a dosing ratio of levalbuterol: albuterol =1:4, levalbuterol showed better outcomes on heart rate changes when compared with racemic albuterol (mean difference=-5.97, p=0.02). However, this difference was dose-dependent as it vanished with equivalent dosing of levalbuterol: albuterol =1:2. Levalbuterol also had a better effect on FEV1 changes (mean difference=3.72, p=0.003). However, there was no statistically significant difference between the two drugs regarding changes in respiratory rate, SpO2 , asthma score , or adverse effects. Conclusion: Levalbuterol and racemic albuterol have almost the same effect on heart rate in asthmatic children when they are used in equivalent dosing (levalbuterol : albuterol =1:2).
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Conclusion: Levalbuterol and racemic albuterol have almost the same effect on heart rate in asthmatic children when they are used in equivalent dosing (levalbuterol: albuterol =1:2).

Abbreviations:

B2: Beta-2 adrenergic receptors
bpm: beats per minute
CI: Confidence Interval COPD: Chronic Obstructive Pulmonary Disease
FEV1: Forced expiratory volume in the first second HR: Heart Rate LEV: Levalbuterol
MD: Mean Difference
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
RAC: Racemic albuterol RR: Respiratory Rate
SMD: Standardized Mean Difference SpO2: Peripheral capillary oxygen saturation

Introduction
Inhaled beta-2 (B2) receptor agonists have been the mainstay of asthma treatment for ages. Their major role is to cause smooth muscle relaxation in order to counteract the pathological contraction caused by asthma and other similar conditions.

Among the different B2 agonists in the market, racemic albuterol (RAC) has been the most frequently used drug. It is a chiral formulation consisting of an equal mixture (1:1) of two mirror-image isomers (enantiomers), (R-) albuterol and (S-) albuterol. On the other hand, Levalbuterol (LEV) emerged recently as a pure (R-) enantiomer inhaled B2 agonist.

These two drugs (RAC and LEV) have been compared pharmacologically by several studies over the last few years due to their enantiomers difference. According to some studies, (R-) enantiomer and (RS-) enantiomer are comparable on a 2:1 potency ratio for both bronchodilatory and adverse effects. Also, it was found that (R-) enantiomer affinity towards B2 adrenergic receptors is 100 folds stronger than the (S-) enantiomer.

Nonetheless, what really intriguing about this matter is that the comparing studies have resulted in relatively conflicting findings. Qureshi et al established that the (R-) enantiomer is responsible for most of the B2 adrenergic effects in the bronchial musculature as well as the metabolic and cardiac side effects, and that (S-) enantiomer is pharmacologically inert. This recent belief, however, was rejected by many recent studies that denied the inertness of (S-) enantiomer. For instance, Skoner et al found that the (S-) enantiomer may oppose the bronchodilatory effects of (R-) enantiomer in RAC—a totally opposite finding of Qureshi et al.

Furthermore, (S-) enantiomer showed additional affinity to B1 adrenergic receptors posing a greater clinical challenge, especially when dealing with an asthmatic patient with cardiovascular disease. This poor selectivity of (S-) enantiomer towards beta-adrenergic receptors can cause increased cardiac side effects (e.g., heart rate changes (HR)) in racemic albuterol in comparison with levalbuterol.

Cardiologists routinely treat cardiac patients presenting with a concomitant bronchoconstrictive pathology. However, the data in the literature concerning the cardiac effects of the two most commonly used drugs for this scenario (i.e., RAC and LEV) have been only single clinical trials and most of them included only a small number of patients. In the light of these aforementioned facts, there has been an insisting need for stronger evidence that combines all of these findings and fills this knowledge gap; as the HR difference between LEV and RAC is of paramount importance in clinical practice when dealing with a cardiac patient requiring nebulizing therapy with one of the drugs.

This systematic review gathers all evidence from all randomized controlled trials comparing the safety and efficacy between albuterol (RS-enantiomers) and levalbuterol (R-enantiomer) in the treatment of asthma patients. Our main goal is to examine the cardiac side effects, if any, of these two drugs as well as compare their efficacy in asthmatic patients.

**Methods**

**Eligibility criteria:**

Inclusion criteria included any clinical trial reporting the effects of RAC on HR compared with LEV in a population of asthmatic children.

**Exclusion Criteria:**

Exclusion criteria included any in-vitro or animal studies, studies with duplicated or overlapping data, reviews, conference abstracts, or unreliably extracted or incomplete data. Papers that did not report heart rate as an outcome were also excluded. Studies of hemodynamically unstable patients, patients with an evident concurrent cause that can cause heart rate changes (e.g., anxiety), or patients on beta-antagonist therapy were excluded. Clinical trials were also excluded if one arm of the trial is given a drug that affects the heart rate. However, the study was included if both arms received the same drug with the exact same dosage.

**Information Sources:**
Searching criteria included five online databases until September 13, 2021: PubMed, SCOPUS, Wiley Online Library, Web of Science, and Cochrane Library. Manual search was also performed to identify possibly missed included studies. The manual search included the references, the “Related articles” section on Google Scholar, and the “Similar articles” section on PubMed of the included studies.

Selection process:
Two independent authors scanned the titles and abstracts of the studies resulted from databases search to assess for eligibility. Full-text screening of the included studies was done by two authors as well to make sure they are still eligible. Any discrepancies between the two authors’ decisions in the last two steps were solved by discussion or through a third author. The selection process is visualized using the “Preferred Reporting Items for Systematic reviews and Meta-Analyses” (PRISMA) flow diagram (Figure 1).

Data collection process and data items:
After careful reading of several included studies, extraction sheet was developed using the Microsoft Excel program 16. Two independent authors extracted data from the included studies into the extraction sheet. A third author checked the extracted data and solved any discrepancies or mistakes.

The primary outcome was heart rate change after treatment. Secondary outcomes were respiratory rate, FEV1 peak percent change, potassium serum level, SpO2 peak change, asthma score, and adverse effects.

Study risk of bias assessment:
Two independent authors assessed the risk of bias in the included studies using the “Cochrane Risk of Bias Tool for Randomized Controlled Trials”. Discrepancies were solved by discussion or through a third author.

Effect measures and synthesis methods:
For continuous variables (heart rate, respiratory rate, FEV1 percent, potassium levels, asthma score), mean difference (MD) with a 95% confidence interval (CI) was used to report the results. For dichotomous outcomes (adverse effects), risk ratio (RR) with a 95% CI was used. For the purpose of meta-analyses, heterogeneity among studies was evaluated by inspection of the forest plots and through \(\chi^2\) and \(I^2\). p-value of >0.05 or \(I^2\) greater than 50 was considered as an indication of heterogeneity. Therefore, a random effect model was adopted in cases where heterogeneity is significant. Cochrane Review Manager “RevMan” was used to conduct all meta-analyses included in this review. Other statistical processes, were performed using the Microsoft Excel 16 program.

Certainty assessment:
Sensitivity analysis was conducted when required to examine the effect of individual studies on the total result.

Results

Search Results:
Primary search of the aforementioned databases has found 120 records. The manual search of the possible included studies yielded four more records. Duplicate removal resulted in 68 remaining records. After the two-step screening process, only eight studies were included in the final review, seven of them were eligible for meta-analysis. Further details are shown in the PRISMA chart (Figure 1).

Characteristics of the included studies:

All studies were randomized controlled clinical trials except for Barkiya2016 which was a non-randomized clinical trial. Five studies out of the eight were based in the USA (Gawchik1999, Milgrom2001, Skoner2005,
Qureshi2005, Wilkinson2011) two studies in India (Punj2009, Barkiya2016), and one study in Bangladesh (Rahman2012). Further details concerning each study are available in Table 1.

Risk of bias assessment:
The risk of bias in the included studies was assessed using the Cochrane Collaboration’s tool for assessing the risk of bias. Although Barkiya2016 had a high risk of bias regarding most of the domains, most studies appeared to have an overall low risk of bias. Gawchik1999, Punj2009, Qureshi2005, Rahman2012, and Wilkinson2011 were assessed as having a low risk of bias regarding random sequence generation and allocation concealment. On the other hand, Barkiya2016 had a high risk of bias in both domains, Milgrom2001 had a high risk of bias regarding random sequence generation, and Skoner2005 was judged unclear for both. All included studies were assessed as having a low risk of attrition bias and reporting bias. Further information in this regard can be found in Figure 2 and Supplementary Material 1.

Study outcomes:

Heart Rate changes:
All of the included studies reported heart rate (HR). However, multiple studies reported HR at different times and with different doses. Initially, a meta-analysis was conducted to compare the peaks of mean heart rate changes between the albuterol group and the levalbuterol group regardless of the time of measurement and the doses of the drugs. It showed that levalbuterol had statistically-significant fewer effects on heart rate when compared with albuterol (MD = -5.97, 95% CI [-10.84, -1.1], p = 0.02, I²=87%, N= 7) (Figure 3). However, a subsequent meta-analysis including only studies comparing equivalent doses of levalbuterol and albuterol (LEV: RAC = 1:2) revealed no statistically significant difference between these two drugs on HR (MD = -0.7, 95% CI [-2.79, 1.39], p = 0.51, I²=65%, N= 3) (Figure 4).

To further investigate the association between HR and dosing, a meta-analysis was conducted to compare all the studies that used LEV & RAC with a ratio of 1:4 (the most common non-equivalent dosing). The latter showed a statistically significant decrease in HR effect in the LEV group when compared with the RAC group in this dosing ratio (MD = -9.67, 95% CI [-15.49, -3.85], p = 0.001, I²=85%, N= 5) (Figure 5). Unfortunately; Gawchik1999 did not report the standard deviation for any of the continuous outcomes including heart rate, so it was excluded from all meta-analyses. Nevertheless, it showed similar results to our meta-analysis, as the effect difference on HR between LEV and RAC was dose-dependent and almost vanished with equivalent dosing.

Potassium changes:
Four studies reported potassium levels before and after therapy (Rahman2012, Punj2009, Milgrom2001, Barkiya2016). A meta-analysis comparing the mean difference in potassium level changes between the two groups showed that RAC had a statistically significant greater lowering effect on potassium levels than that of LEV (MD = 0.51, 95% CI [0.10, 0.93], p = 0.02, I²=84%, N= 4) (Supplementary Material 2). It also should be noted that all of these studies used inequivalent doses of the drugs with a ratio of LEV: RAC = 1:4. Gawchik et al. had supporting results as the potassium difference varied according to the dosage ratio.

Respiratory Rate changes:
Five studies reported the changes in respiratory rate (RR) following therapy (Barkiya2016, Punj2009, Qureshi2005, Wilkinson2011, Rahman2012). A meta-analysis showed the absence of any statistically significant difference between LEV and RAC in this regard (MD = -0.93, 95% CI [-2.82, 0.95], p = 0.33, I²=77%, N= 5) (Supplementary Material 3). The dosing among the studies was various. Barkiya2016, Punj2009, and Rahman2012 used inequivalent dosing (LEV: RAC 1:4); while Qureshi2005, and Wilkinson2011 used equivalent dosing (LEV: RAC 1:2).

SpO2 Changes:
Five studies reported SpO\textsubscript{2} changes after the administration of LEV and RAC (Barkiya2016, Punj2009, Qureshi2005, Wilkinson2011, Rahman 2012). A meta-analysis showed that LEV and RAC did not have any statistically significant difference regarding SpO\textsubscript{2} changes (MD = -0.11, 95% CI [-0.80, 0.58], p= 0.75, I\textsuperscript{2}=0%, N= 5) (Supplementary Material 4). Dosing in SpO\textsubscript{2} change outcome was similar to that in RR change.

**FEV\textsubscript{1} changes:**

Four studies reported FEV\textsubscript{1} changes of %predicted value following treatment with LEV or RAC (Gawchik1999, Barkiya2016, Milgrom2001, Rahman2012); One study (Qureshi2005) reported the mean percent changes from baseline FEV\textsubscript{1}. Milgrom2001 did not clearly define how they reported this outcome, so a sensitivity analysis was conducted in this regard. The meta-analysis showed that LEV had statistically significant better effect on FEV\textsubscript{1} (measured as change of %FEV\textsubscript{1} of predicted) when compared with RAC (MD = 3.79, 95% CI [1.27, 6.31], p= 0.003, I\textsuperscript{2}=0%, N= 4). Qureshi2005 found no statistically significant difference (Supplementary Material 5). The sensitivity analysis for Milgrom2001 did not alter the results of the meta-analysis regarding both types of FEV\textsubscript{1} reporting methods. Wilkinson2011 was excluded from this meta-analysis due to the vague number of participants; however, the reported results in this study are conflicting with the results of the meta-analysis (RAC had remarkably more effect on FEV\textsubscript{1}). One study (Qureshi2005) reported the mean percent change from baseline FEV\textsubscript{1}; no statistically significant difference was detected (Supplementary Material 5).

The dosing among these studies was variable as Barkiya2016, Milgrom2001, and Rahman2012 used inequivalent doses with LEV: RAC 1:4; Qureshi2005, and Wilkinson2011 used equivalent dosing with LEV: RAC 1:2; and Gawchik1999 used multiple equivalent and inequivalent doses in the study.

**Asthma Score:**

Three studies reported asthma score changes following treatment (Barkiya2016, Punj2009, Rahman2012). A meta-analysis, showed no statistically significant difference between asthma score changes in LEV when compared to RAC (MD = 0.01, 95% CI [-0.40, 0.42], p= 0.95, I\textsuperscript{2}=0%, N=3). Two studies reported asthma score percent changes from baseline (Qureshi2005, Wilkinson2011). A subsequent meta-analysis showed also no statistically significant difference between the two groups. (MD = 7.27, 95% CI [-5.46, 20.01], p= 0.26, I\textsuperscript{2}=95%, N=2) (Supplementary Material 6). Dosing in asthma score change outcome was similar to that in RR change.

**Adverse effects:**

Only two studies investigated the adverse effects of LEV or RAC therapy (Qureshi2005 and Wilkinson2011). The main reported adverse effects were nausea or vomiting, and headache. Two subsequent meta-analyses found no statistically significant difference between these two adverse effects between LEV and RAC (RR = 0.74, 95%CI [0.42,1.32], p= 0.32, I\textsuperscript{2}=45%, N=2) (Supplementary Material 7), (RR = 1.88, 95%CI [0.85, 4.18], p= 0.12, I\textsuperscript{2}=0%, N=2) (Supplementary Material 18) for nausea or vomiting, and headache respectively.

Multiple other adverse effects were reported in one of the two studies rather than in both of them. This included jitteriness, a drop in K\textsuperscript{+} levels below 3 mEq/L, lightheadedness, tremulousness, tachycardia, and high temperature. However, no statistically significant difference was found between LEV and RAC regarding any of these adverse effects (Data not shown).

**Discussion**

Cardiac side effects discrepancy between LEV and RAC has been a matter of debate in the medical literature for several years. As far as we know, the literature still lacks strong evidence in this regard, because most of the published articles up to this point are clinical trials with only a small number of participants and with relatively conflicting results. In the light of this literature gap, there was a paramount need for an article that combines the results of these clinical trials to establish better evidence that will guide our clinical practice. In this systematic review and meta-analysis, data from 8 clinical trials were analyzed comparing the effects
of LEV versus RAC on heart rate in pediatric asthmatic patients. Collectively, our article included a total of 1002 patients from eight different trials.

The initial results of the meta-analysis that compared HR changes between RAC and LEV regardless of the dosing showed a statistically significant less effect on heart rate when using LEV in comparison with RAC. However, most studies in the medical literature used inequivalent doses of the two study drugs which may have caused LEV to appear less effective. To check this theory, a meta-analysis was conducted to compare all the studies that used a LEV to RAC ratio of 1:4 (the most commonly used ratio). The latter showed even much less effect on HR of LEV in comparison with RAC. Furthermore, the meta-analysis revealed no statistically significant difference between their effects in the studies that used equivalent doses of both drugs (LEV to RAC = 1:2).

Upon searching the literature, another systematic review assessed the efficacy and safety of these drugs. Jat et al. studied the effects of LEV and RAC on various vital signs and mentioned no statistically significant difference between the two drugs regarding HR changes. Nevertheless, they based their conclusions on the results of only two trials. In addition, their population was not limited to pediatric patients as they included articles studying participants of all ages.

Carl et al. also studied HR changes of LEV versus RAC in pediatric patients presenting with acute asthma exacerbation. They found no statistically significant difference between the two drugs in this population. However, this trial could not be included in our study as they did not mention HR before treatment nor HR changes. The same results were found in Bio et al., which studied the effects of these two drugs on hospitalized pediatric patients. The downsides of this study were the discrepancy in the drug doses used for treatment and some of the patients were already tachycardiac at the time of receiving the nebulizations. This article was excluded because the participants were not asthmatic.

Kelly et al. studied the difference between LEV and RAC on HR in pediatric cardiology patients. They found a negligible mean difference (0.6 beats per minute (bpm)) in HR changes between the two drugs, with RAC being the one with the greatest HR increase. Analysis of HR changes in the congestive heart failure subgroup showed even a smaller mean difference (0.3 bpm) between the two drugs. They did analyses for other subgroups, however, the number of patients in each one is small (i.e., less than ten).

On the other hand, Brunetti et al. did the same investigation on adult patients with COPD or asthma. They found no significant difference between LEV and RAC on HR changes in this population.

Thus, we can surely state that our article is the first systematic review to meticulously investigate differences of HR changes between LEV and RAC in asthmatic pediatric patients. However, our study had a few limitations: the trials included in this systematic review used varied timings to measure the outcomes. Although most of them reported heart rate 15 minutes after the end of treatment, there have been several exceptions. For example, in Punj2009 they only mentioned measuring heart rate after the end of treatment, we considered the timing as “after 15 minutes”. In Milgrom2001 and Skoner2005, HR was reported on multiple hospitalization days (on days 1 and 21), we evaluated the data recorded on the first day only. Also; while analyzing the data of Qureshi2005, Milgrom2001, Skoner2005, and Wilkinson2011, some patients received more nebulizations than the others. We used the outcome of the first treatment only and omitted latter nebulizations. Another statistical problem is that the results of Qureshi2005, Wilkinson2011, and Milgrom2001 were represented in the form of the 5- to 95- percentile range.; which was solved by considering 5 and 95 results as 0 and 100 respectively. Lastly, the results of Gawschik1999 were omitted from all numerical analyses due to the absence of standard deviation data in their paper. Another limitation to highlight is that this study included only pediatric patients; as the studies in adults are very few and disparate. This might pose a question mark on the generalizability of the results in the adult population. Therefore, more studies concerned with the adult population need to be conducted to evaluate the generalizability of the results.

**Conclusion**

The cardiac side effects of LEV and RAC seem to be dose-dependent. In the most commonly used dosing
ratio of LEV: RAC = 1:4, LEV is more favorable when HR is a concern. However, when using equivalent
dosing (LEV: RAC = 1:2), no significant difference between the drugs was found.

DECLARATION:

Ethics Statement:

This Article is performed correspondingly with the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly work in Medical Journals.

Availability of Data and Material:

The data underlying this article are available in the article and in its online supplementary material.

Conflict of interests:

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References

Figures:

Figure 1: PRISMA chart elaborating the various subsequent steps of study selection.

Figure 2: Summary of risk of bias assessment in all studies.

Figure 3: A meta-analysis of all studies that reported heart rate changes difference between levalbuterol and albuterol.

Figure 4: A meta-analysis of studies that reported heart rate changes with equivalent doses of both study drugs.

Figure 5: A meta-analysis of studies that used RAC to LEV ratio of 1:4 comparing the difference between mean heart changes after treatment.

Tables:

Table 1:

Title: Study’s Characteristics. Legend: This table details the characteristics of all included studies sorted ascendingly according to the date of publication.

Supplementary Materials:

Supplementary Material 1: A summary of risk of bias assessment in all studies.

Supplementary Material 2: A meta-analysis of all studies that reported potassium changes after therapy.

Supplementary Material 3: A meta-analysis of all studies that reported the RR changes following therapy with LEV and RAC.

Supplementary Material 4: A meta-analysis of all studies that reported SpO2 changes following LEV and RAC treatment.

Supplementary Material 5: A meta-analysis of all studies that reported FEV1 Changes following therapy. A: FEV1 changes after considering FEV1 reported a change in percent of predicted in Milgrom2001. B:
FEV1 changes after considering FEV2 reported as a percent change in Milgrom2001. C: FEV1 changes after excluding Milgrom2001.

**Supplementary Material 6**: A meta-analysis of all studies that reported asthma score changes following treatment.

**Supplementary Material 7**: A meta-analysis of studies reporting the incidence of nausea or vomiting as an adverse effect.

**Supplementary Material 8**: A meta-analysis of studies that reported the incidence of headache as an adverse effect.
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- **Random sequence generation (selection bias)**
- **Allocation concealment (selection bias)**
- **Blinding of participants and personnel (performance bias)**
- **Blinding of outcome assessment (detection bias)**
- **Incomplete outcome data (attrition bias)**
- **Selective reporting (reporting bias)**
- **Other bias**
Table 1.docx available at https://authorea.com/users/512554/articles/589043-the-cardiac-side-effects-of-levalbuterol-versus-albuterol-in-pediatric-patients-presenting-with-acute-asthma-attacks-a-systematic-review-and-meta-analysis