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Review Article

Sulphonylurea Use in Diabetic Patients with Melioidosis: A Systematic Review

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I N F O

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A B S T R A C T

Introduction: Diabetes is a common comorbidity among patients with melioidosis. Melioidosis, is an infectious disease caused by *Burkholderia pseudomallei.* Current literature shows a conflicted view regarding the interactions between sulphonylurea medications and susceptibility and severity of B. pseudomallei infections. We conducted a systematic review to determine the effect of sulphonylurea medications on diabetic patients with melioidosis.

Methods: We included randomized controlled trials, prospective and retrospective cohort studies that compared health outcomes among patients with diabetes and melioidosis who were taking sulphonylurea medication with those who were not. Our primary outcome was mortality, while secondary outcomes were development of complications such aswere hypotension, septicemia and respiratory distress. The methodological quality of included studies was investigated using the checklist by Downs and Black. Data were synthesized as risk ratios (RR) with 95% Confidence Intervals (CI) using random effects model.

Results: We included three observational studies enrolling a total of 1,349 patients. We did not find evidence for a difference in mortality among patients suffering with melioidosis and diabetes receiving sulphonylurea medications compared with patients not receiving sulphonylurea medications (RR: 0.63 (95 % Cis 0.22-1.85) p=0.41). We also did not find any significant differences in hypotension (RR: 0.81 (95% Cis 0.25-2.62) p=0.73), respiratory distress (RR: 0.66 (95%Cis 0.34-1.29) p=0.23), or septicemia (RR: 0.80 (95% Cis 0.45-1.42) p=0.45) between the two groups.

Conclusion: Given the high comorbidity rate of melioidosis and diabetes and the use of sulphonylureas as a first line treatment, we believe a far more thorough investigation of the effect of sulphonylurea medications on mortality and complications from melioidosis is warranted.

Keywords: Diabetes, Glyburide, Glipizide, Melioidosis, Sulphonylurea, Thailand

Introduction

Melioidosis, also known as Whitmore's disease, is an infectious disease caused by *Burkholderia pseudomallei,* a gram-negative bacterium commonly found in soil and surface water. Clinical presentations of this disease include bacteremia, abscesses in any organ system, or soft tissue infection. The clinical course can range from mild to severe fulminant septicemia. Additional comorbidities such as type 2 diabetes mellitus, retrovirus infection, thalassemia, collagen vascular disease, and chronic renal disease have been associated with the severity of its presentation.[1]

Melioidosis is highly endemic to northeastern Thailand and northern Australia. It can also occur in people who travel to other high-risk areas such as South and Central America, a few Pacific and Indian Ocean islands, and some countries in Africa. Over 7000 cases have been reported in Thailand alone and the fatality rate for melioidosis ranges from 14 to 40%.[2] It can be as high as 80% if the proper treatment is not prescribed.[3] The transmission of this environmental saprophyte bacterial occurs through three routes: respiratory through inhalation, cutaneous through skin abrasions, and gastrointestinal through consumption of contaminated water.[4]

International melioidosis treatment guidelines recommend a two-phase approach. The first phase is 10 to 14 days of intravenous antibiotic therapy, termed the intensive phase. Antibiotics are not usually stopped until body temperature has returned to normal for more than 48 hours. The second phase consists of 3 to 6 months of oral therapy, termed the eradication phase.[5] A major challenge with treating melioidosis is its resistance to many broad-spectrum antibiotics including penicillin, ampicillin, gentamycin, and first and second generation cephalosporins. Nevertheless, most strains remain resistant to beta-lactams, ceftazidime, imipenem, meropenem, piperacillin, amoxicillin-clavulanate, ceftriaxone, and cefotaxime.[6]

Type 2 diabetes is a common comorbidity, with over 50% of patients with melioidosis also being diagnosed with diabetes mellitus.[7] Although type 2 diabetes has been traditionally associated with populations living in High Income Countries (HIC), in the last few years the incidence of this non-communicable disease has been accelerating in Low and Middle Income Countries (LMIC).[4] This has resulted in the increase of type 2 diabetes as a comorbidity in melioidosis, an endemic disease of LMIC where populations are exposed to water in rice fields.

There have been concerns that sulphonylurea medications such as glyburide, a commonly prescribed treatment for diabetes, may increase susceptibility and severity of *B. pseudomallei* infections.[8,9] However, other sources have suggested that sulphonylurea medications may have a protective effect from infection in diabetic patients.[10] We conducted a systematic review to determine the effect of sulphonylurea medications on diabetic patients with melioidosis. Our primary outcome was mortality, while secondary outcomes were hypotension, septicemia, and respiratory distress.

Materials and Methods

Systematic Review and Meta Analysis

Inclusion and Exclusion Criteria

Randomized Controlled Trials (RCTs), prospective and retrospective cohort and case-control studies that compared outcomes of patients with type-2 diabetes mellitus and melioidosis who were taking oral sulphonylurea medication with those who were not were eligible for inclusion in our systematic review. Studies in any language up to June 2018 were included. Studies that reported data using mouse models or human cells in vitro were excluded.

Types of Interventions

The treatment group was defined as patients taking any medication classified as a sulphonylurea. The control group was made up of patients that were not on sulphonylurea-containing medication regimen.

Outcomes

Our primary outcome was overall survival (OS).

We examined three major secondary outcomes. The first was the number of patients who experienced hypotension. Next, we compared the number of patients who experienced respiratory failure. Our final secondary outcome was the number of patients who had septicemia.

Search Methods for Identification of Studies

We searched the following databases:

- MEDLINE (search date: June 2018)
- EMBASE (search date: May 2018)
- TRIP (search date: May 2018)
- Web of Science (search date: June 2018)

Search Terms

We used the following search terms in the abovementioned databases:

- Melioidosis, sulphonylurea and diabetes
- Melioidosis and (glibenclamide or glipizide or glyburide)

Searching Other Resources

Data were unclear for one included study and we contacted the study authors for clarification. The principal investigator shared de-identified raw data regarding health outcomes in sulphonylurea vs non-sulphonylurea patients for use in our analysis.[11]

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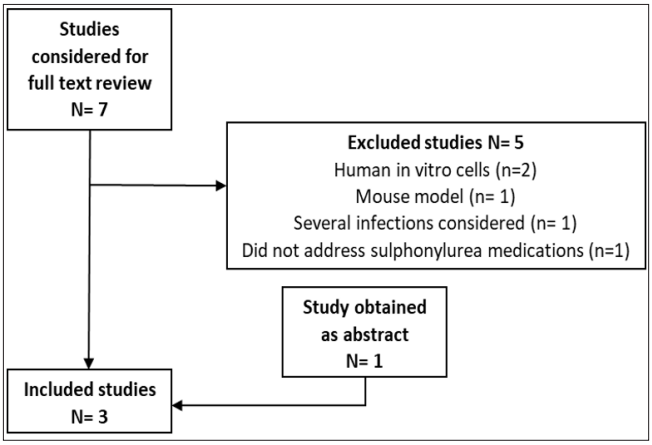

Figure 1.Study flow diagram

Data Collection and Analysis

Study Selection

Review authors SP and AP independently read the full texts of all collected studies to determine their eligibility for inclusion in this review. Any disagreements were resolved by consensus, and studies marked for inclusion were rechecked by the senior author (RM). Search strategies, data collection, and other details are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[12]

Data Extraction and Management

SP and AP extracted all data and compiled it into a Microsoft Excel spreadsheet. One researcher extracted data into Review Manager 5 software, and the other checked the entries for accuracy. In addition to the outcomes extracted that are listed above, we also collected data regarding location of study, description of withdrawals and dropouts, drug and dose, length of treatment, length of follow-up, and total number of participants.

Assessment of Risk of Bias in Included Studies

Two review authors independently assessed all included studies for their risk of bias according to the Downs & Black checklist for study quality, then convened and arrived at a consensus score for each study.[13] Each of the 27 questions on the checklist were answered with a number based on the following three-point scale: 1=No; 2=Partial or uncertain; 3=Yes.

A higher summed score indicated potentially a lower risk of bias.

Data Items and Summary Measures

All data including the primary and secondary outcomes collected were dichotomous counts.

Statistical analysis

Data were summarized as Risk Ratios (RR) with 95% Confidence Intervals (CI) and pooled using a random-effects model in Review Manager 5 software by the Cochrane Collaboration.

Results

Search and Description of Studies

Our initial search in February 2018 yielded seven studies for consideration for this review. One study was excluded because it examined the impact of sulphonylurea medications on risk of sepsis caused by several infectious organisms, not specifically *B. Burgdorferi.*[14] One study was excluded because it did not address the effect of sulphonylurea medications specifically.[15] Three other studies were excluded because they examined human cells in vitro or used mouse models.[9,16,17] Two studies which matched our inclusion criteria were found in a formal search of published literature, while a third study was obtained as an abstract from a USF Health Research Day for a total of three studies in our meta-analysis (Figure 1).

Koh GC et al. compared the health outcomes of 1160 patients with melioidosis. Patients were classified into three groups: no diabetes, confirmed diabetes diagnosis, and hyperglycemia.[11] We contacted Dr. Koh for additional data to divide the "confirmed diabetes diagnosis" into sulphonylurea and non-sulphonylurea groups, and compared outcomes between them. Patients discharged alive from the hospital at 28 days were assumed to have survived and patients who self-discharged against medical advice were censored on the day of discharge.[11]

Both Liu X et al.[7] and Chandra V et al. studied diabetic melioidosis patients in groups of "sulphonylurea" and "without sulphonylurea", with samples of 74 and 115 patients, respectively.[7,18] We extracted data on mortality, as well as numbers of patients that experienced hypotension, respiratory distress, and septicemia. Chandra V et al. used a logistical regression model and described mortality in terms of all-cause mortality.[18] Liu X et al. used chi-squared test or Fisher exact probability where appropriate for mortality measures. All patients were followed up for at least 12 weeks from the start of treatment.[7]

Risk of Bias Assessment

Overall the methodological quality of included studies was optimal. Specifically, Koh GCKW et al. had a total score of 73, Liu X et al. had a total score of 69 and Chandra V et al. had a total score of 61.

A higher score suggests a lower risk of bias significantly affecting the results of the study. None of the included studies reported blinding of patients and researchers or randomized intervention assignment, but that was to be expected given that all were either retrospective case-control or prospective cohort models and it did not affect

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the validity of their results. Koh GCKW et al. was the only study that reported relevant details regarding patients lost to follow-up.[11] Additionally, Chandra V et al. did not report on adverse events or adjustments for confounders.[18]

Synthesis of Results

We found no evidence for a difference in mortality among patients suffering with melioidosis and diabetes receiving sulphonylurea medications compared with patients not receiving sulphonylurea medications (RR: 0.63 (95% Cis 0.22-1.85) p=0.41) (Figure 3). We also did not find any significant differences in hypotension (RR: 0.81 (95% Cis 0.25-2.62) p=0.73), respiratory distress (RR: 0.66 (95% Cis 0.34-1.29) p=0.23), or septicemia (RR: 0.80 (95% Cis 0.45-1.42) p=0.45) between the two groups.

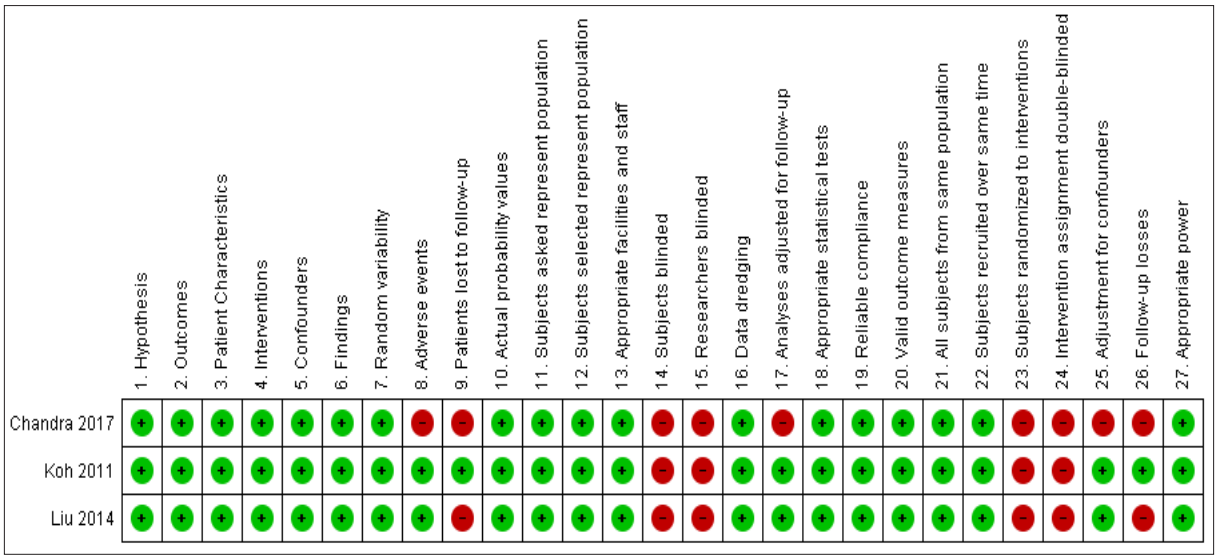

Figure 2.Risk of bias assessment. Green indicates a "low risk of bias" while red indicates "high risk of bias"

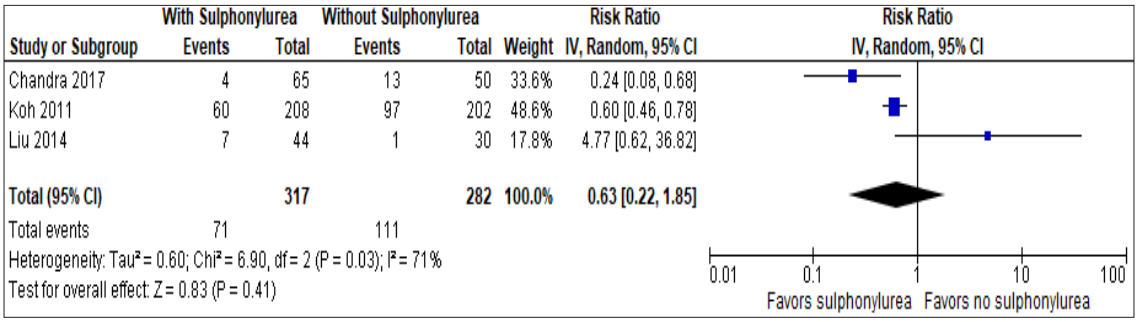

Figure 3.Pooled risk ratio for mortality. The summary estimate (risk of mortality with sulphonylurea versus without sulphonylurea) from individual studies is indicated by rectangles with lines representing 95% CI. The summary pooled estimate is represented by the diamond with lines representing 95% CI

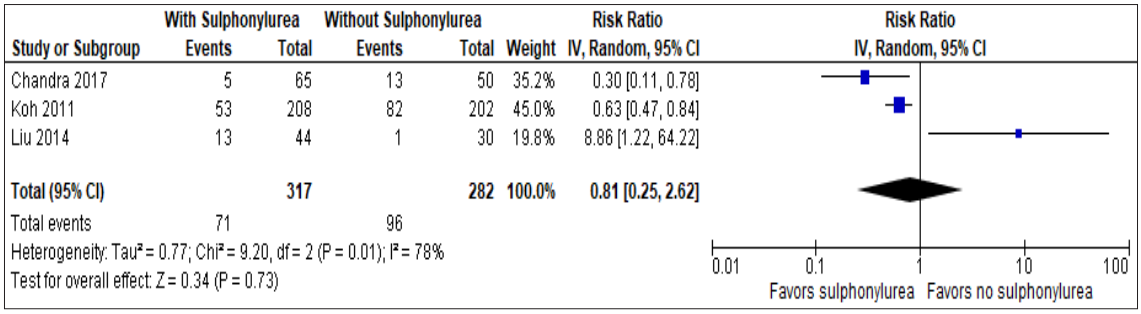

Figure 4.Pooled risk ratio for hypotension. The summary estimate (proportion of patients experiencing hypotension with sulphonylurea versus without sulphonylurea) from individual studies is indicated by rectangles with lines representing 95% CI. The summary pooled estimate is represented by the diamond with lines representing 95% CI

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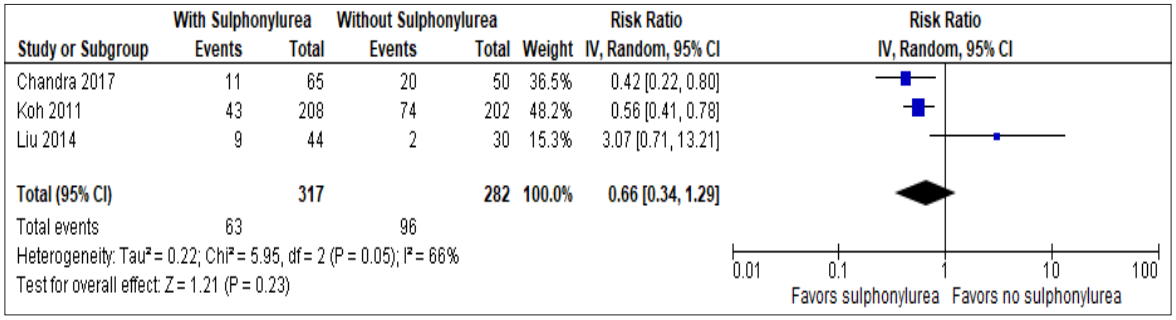

Figure 5.Pooled risk ratio for respiratory distress. The summary estimate (proportion of patients experiencing respiratory distress with sulphonylurea versus without sulphonylurea) from individual studies is indicated by rectangles with lines representing 95% CI. The summary pooled estimate is represented by the diamond with lines representing 95% CI

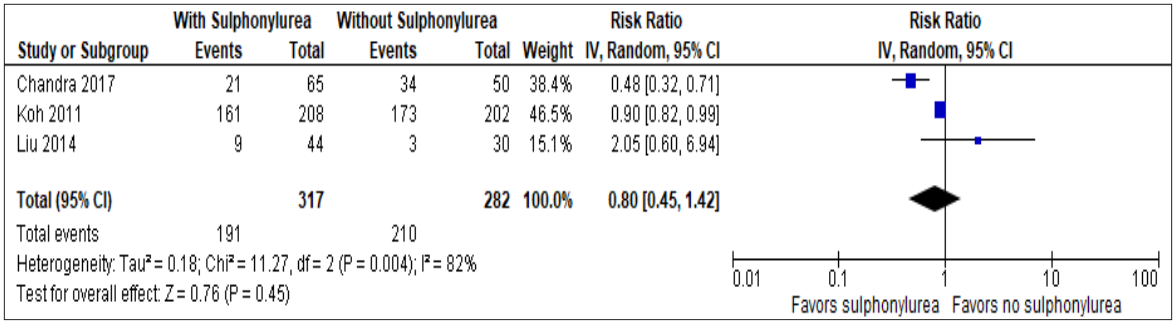

Figure 6.Pooled risk ratio for septicemia. The summary estimate (proportion of patients experiencing septicemia with sulphonylurea versus without sulphonylurea) from individual studies is indicated by rectangles with lines representing 95% CI. The summary pooled estimate is represented by the diamond with lines representing 95% CI

Discussion

Both Koh GCKW et al. and Chandra V et al. reported finding an association between sulphonylurea containing diabetes treatment and survival benefit while Liu X et al. reported that the treatment was correlated to a more severe clinical course of melioidosis, especially relating to hypotension.[7,11] In this systematic review, we ultimately did not find a statistically significant difference in primary or secondary outcomes between melioidosis patients with diabetes taking sulphonylurea medications and those who were not.

Koh GCKW et al. and Liu X et al. both agree that glyburide has an anti-inflammatory effect, but disagree on the clinical significance of the resulting inhibition of immune response to infection versus attenuation of autoimmune damage.[7, 11] According to Lamkanfi M et al. glyburide causes inhibition of the cryopyrin-dependent inflammasome.[8] Koh GCKW et al. suggest that this stops overactivation of interleukin (IL)-1β and IL-18 as well as neutrophil recruitment, preventing associated respiratory distress and tissue damage.[11] However, Liu X et al. points out that this causes an increased susceptibility to infection that is ultimately a stronger effector of clinical outcome.[7] It has been hypothesized that glyburide may lower free glutathione (GSH) intracellular levels of Polymorphonuclear Neutrophils (PMN) of patients treated with this drug. These low GSH levels may interfere with PMN functions such as cytokines production, migration, and apoptosis.[16]

Study-level limitations universally included the inability to blind researchers or patients to the interventions being measured. Due to the less organized healthcare system in Thailand, researchers often experienced difficulties obtaining data on treatment timelines and records of patient follow-ups. Nonetheless, only one study did not specify its efforts to adjust for confounding variables.[18] Major review-level limitations of this study include, first and foremost, the small sample size of studies available for meta-analysis. Due to the health concern in question being centered around Southeast Asia, we considered the possibility that additional papers in languages other than English could exist on the subject and accordingly we did include EMBASE, a database with a more international reach, in our search. The lack of available research also limited our review to an analysis of sulphonylurea medications as a whole, rather than separately doing analyses of each medication. This is significant because glipizide has not been shown to have the same inhibitory effect on the cryopyrin-dependent inflammasome that glyburide possesses.[8]

Melioidosis is highly endemic and is associated with high mortality in Southeast Asia. Along with the prevalence of comorbid diabetes and the continued use of

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sulphonylurea medications as a first-line treatment for diabetes medication, we believe a far more thorough understanding of the effect of sulphonylurea medications on mortality and complications from melioidosis is warranted. As of 2018, only two published clinical studies on the possibility of these drugs causing serious adverse effects in a significant population of Asian diabetics exist.[7, 11] While we acknowledge the difficulty of collecting large volumes of data in developing regions, it is necessary to ensure safety in such a vulnerable patient population.

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Declarations of Interest

The authors do not have any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Ethical Approval

All work was carried out in accordance with The Code of Ethics of the World Medical Association and the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals published by the International Committee of Medical Journal Editors. As this was a systematic review of previously conducted research, there was no human experimentation or use of protected health information (PHI) in this study.

Conflict of Interest: None

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