Efficacy and safety of ranolazine in the treatment of type 2 diabetes mellitus: a Meta-analysis

Ji Huanhuan1, Song Lin1, Meng Long2, Yang Bin1, Xie Hongmeng1, Che Keke1, Gu Rong1, Jia Yuntao1
1. Department of Pharmacy, Children's Hospital of Chongqing Medical University
2. Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing Key Laboratory of Pediatrics, The First Affiliated Hospital of Chongqing Medical University

Abstract
Objective: To evaluate the efficacy and safety of ranolazine in the treatment of diabetes mellitus type 2 (T2DM). Methods: CENTRAL, Medline, Embase, CNKI, VIP, CBM, Wanfang database, WHO Clinical Trials Registry Platform and ClinicalTrials.gov were searched. The quality of included randomized controlled trials was assessed according to the Cochrane Collaboration system review and then Meta-analysis was performed using RevMan 5.2. Results: A total of 7 randomized controlled trials were enrolled including 3131 patients. Meta-analysis showed that ranolazine (0 000 mg bid) monotherapy compared with placebo resulted in a significant reduction in HbA1c (MD = -0.55, 95% CI = -0.73 to -0.37) and fasting plasma glucose (FPG) (SMD = -0.34, 95% CI = -0.53 to -0.15) in T2DM patients. As an add-on interaction with antidiabetes compared with placebo, ranolazine (0 000 mg bid) resulted in a significant reduction in glycosylated hemoglobin (HbA1c) (MD = -0.47, 95% CI = -0.62 to -0.36). Conclusion: In the treatment of T2DM, ranolazine (0 000 mg bid) could be used as monotherapy or with antidiabetes as add-on interaction to help reduce HbA1c and FPG levels, and is safe and well tolerated.
ranolazine resulted in a significant reduction in HbA1c with T2DM. The SMD of T2DM patients was 0.11 with a 95% CI of -0.26 to 0.48 (P = 0.57). When add-on to antidiabetes ranolazine 500 mg bid compared with trimetazidine elicited a similar reduction in HbA1c (SMD = -0.30, 95% CI = -1.35 to 0.75, P = 0.22). In 2 h postprandial 2 hours blood glucose (2hPG) SMD = 0.15 (95% CI = -0.42 to -0.73 with P = 0.60). Ranolazine didn’t increase the risk of hypoglycemia (RR = 1.24, 95% CI = 0.80 to 1.93, P = 0.34).

Conclusion: Ranolazine can effectively reduce HbA1c level by inhibiting glucagon secretion and safe for adults with T2DM.

Key words: ranolazine; diabetes mellitus type 2 (T2DM); Meta-analysis; randomized controlled trial
2.1 结果

采用随机效应模型，考虑到卡方检验把握度不高，本研究根据入排标准，进行定性描述或亚组分析。文献筛选流程及结果如图所示，纳入研究的基本特征见表 1.

表 1 纳入研究的基本特征

<table>
<thead>
<tr>
<th>研究</th>
<th>年份</th>
<th>患者来源</th>
<th>性别</th>
<th>年龄（岁）</th>
<th>糖化血红蛋白（%）</th>
<th>空腹血糖水平（mmol/L）</th>
<th>2hPG水平（mmol/L）</th>
<th>BMI（kg/m²）</th>
<th>HbA1c（%）</th>
<th>FPG（mg/dL）</th>
<th>eGFR【ml/min 1.73 m²】</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pettus 2016</td>
<td>24</td>
<td>North America/India</td>
<td>18</td>
<td>31.3</td>
<td>35.1</td>
<td>8.2</td>
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<td>19.5</td>
<td>6.4</td>
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<tr>
<td>GAOS</td>
<td>21</td>
<td>Eastern Europe/other</td>
<td>22</td>
<td>39.2</td>
<td>33.1</td>
<td>8.4</td>
<td>8.8</td>
<td>17.4</td>
<td>6.8</td>
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<td>60.1</td>
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<tr>
<td>Robert 2015</td>
<td>23</td>
<td>South America/US/India</td>
<td>20</td>
<td>35.5</td>
<td>32.1</td>
<td>8.6</td>
<td>8.9</td>
<td>16.0</td>
<td>6.5</td>
<td>12.0</td>
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<tr>
<td>NCT0163721</td>
<td>25</td>
<td>Unites States</td>
<td>21</td>
<td>37.2</td>
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<td>Pettus 2016</td>
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<td>GAOS</td>
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<td>Sandhlya 2015</td>
<td>28</td>
<td>India</td>
<td>23</td>
<td>35.1</td>
<td>32.1</td>
<td>8.6</td>
<td>8.9</td>
<td>16.0</td>
<td>6.5</td>
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<tr>
<td>Morrow 2009</td>
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<td>Unites States</td>
<td>21</td>
<td>37.2</td>
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<td>8.5</td>
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<td>Adam 2006</td>
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</tr>
</tbody>
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注：① 表示 HbA1c 水平；② 表示 FPG 水平；③ 表示 2hPG 水平；④ 表示 BMI 水平；⑤ 表示 HbA1c 水平；⑥ 表示 eGFR 水平。
2.2 方法学质量评价

方法学质量评价结果如图2所示。仅2...n受
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2.3 Meta

2.3.1 HbA1c

NCT 01163721
Pettus 2016[CAOSE] 7 000 mg bid

Pettus 2016[MAOSE] 5 000 mg bid

Robert 2015 4 000 mg bid

Sandhlya 2015 3 000 mg bid

2 2 2 2 2 2 2

Fig.2 Risk of bias summary

2.3.3 FPG

Morrow 2009

NCT 01163721
Pettus 2016[CAOSE] 7 000 mg bid

Pettus 2016[MAOSE] 5 000 mg bid

Robert 2015 4 000 mg bid

Sandhlya 2015 3 000 mg bid

2 2 2 2 2 2 2

Fig.3 Forest plot of Meta-analysis of FPG level in ranolazine and control groups

2.3.4 HbA1c<7%

NCT 01163721
Pettus 2016[CAOSE] 7 000 mg bid

Pettus 2016[MAOSE] 5 000 mg bid

Robert 2015 4 000 mg bid

Sandhlya 2015 3 000 mg bid

2 2 2 2 2 2 2

Fig.4 Forest plot of Meta-analysis of the success rate of HbA1c<7% in ranolazine and control groups

2.3.2 FPG

Morrow 2009

NCT 01163721
Pettus 2016[CAOSE] 7 000 mg bid

Pettus 2016[MAOSE] 5 000 mg bid

Robert 2015 4 000 mg bid

Sandhlya 2015 3 000 mg bid

2 2 2 2 2 2 2

Fig.3 Forest plot of Meta-analysis of FPG level in ranolazine and control groups

2.3.4 HbA1c<7%

NCT 01163721
Pettus 2016[CAOSE] 7 000 mg bid

Pettus 2016[MAOSE] 5 000 mg bid

Robert 2015 4 000 mg bid

Sandhlya 2015 3 000 mg bid

2 2 2 2 2 2 2

Fig.4 Forest plot of Meta-analysis of the success rate of HbA1c<7% in ranolazine and control groups
In the context of diabetes management, the study evaluated the effectiveness of ranolazine (500 mg bid) in combination with standard antihyperglycemic therapy compared to placebo. The results indicated a significant reduction in 2hPG levels, with a mean difference of 2.02 mg/dL (95% CI: -0.37, 10.91 mg/dL) in the ranolazine group, compared to the placebo group (10.91 mg/dL, 95% CI: -0.37, 10.91 mg/dL). This difference was statistically significant (P = 0.001).

The study also reported a trend towards improvement in insulin levels, with a decrease in fasting insulin levels in the ranolazine group compared to the placebo group. However, the full statistical analysis including effect size, heterogeneity, and statistical significance is not clearly presented in the image.
3 讨论

本次Meta分析结果显示:①纳入RCTs治疗周期均大于12周,雷诺嗪(1000 mg bid)单药治疗可降低HbA1c、FPG、2hPG水平;②在降糖药基础上,雷诺嗪(1000/750 mg bid)可降低HbA1c水平,但无降低FPG、2hPG水平的作用;雷诺嗪(500 mg bid)无降低HbA1c、FPG、2hPG水平的作用;③雷诺嗪(1000 mg bid)可降低空腹及餐后3 h胰高血糖素水平,而无降低体质量、空腹胰岛素及C肽水平作用,雷诺嗪(750/500 mg bid)无相关数据报告;④雷诺嗪不增加低血糖风险,其主要不良事件包括便秘、头晕、头痛、恶心等。

提示雷诺嗪安全性良好,具有一定降糖作用,其降糖疗效可能与剂量及疗程相关,对体质量无影响。

雷诺嗪降糖机制与抑制Na+通道的电活动,阻断胰腺α细胞的钠通道,从而抑制胰高血糖素的释放有关。

在糖尿病动物模型中,雷诺嗪降低HbA1c、高血糖的作用与抑制空腹及餐后胰高血糖素水平相关;雷诺嗪不刺激胰岛素分泌且低血糖时不抑制胰高血糖素释放[14],从机制上解释了雷诺嗪可降低T2DM患者的HbA1c、空腹及餐后胰高血糖素水平,而对空腹胰岛素水平无影响,也不增加低血糖风险。

雷诺嗪降糖作用可能与剂量相关,其用法用量为500~1000 mg每次，2次/d。

本研究显示雷诺嗪起始剂量(500 mg bid)无降糖疗效,但仅纳入1个小样本临床试验,尚需更多研究证实。

本研究显示雷诺嗪与降糖药(格列美脲或胰岛素等)联用有协同降糖作用。但Eckel等[9]报告的二甲双胍(500 mg bid)联合雷诺嗪(1000 mg bid)与二甲双胍(1000 mg bid)联合安慰剂治疗T2DM,HbA1c水平方面两组差异无统计学意义,该结果可能与二甲双胍的剂量差异有关。

最新研究表明二甲双胍降糖作用主要在小肠,降糖疗效与小肠的二甲双胍药物暴露水平相关[15]。从某种意义上讲雷诺嗪减小了二甲双胍的服药剂量。值得注意的是,雷诺嗪与二甲双胍存在药代动力学相互作用,可抑制二甲双胍的肾排泄,从而升高二甲双胍血药浓度[16],而雷诺嗪合并二甲双胍的降糖疗效及其他药物相互作用尚待进一步研究。

本次Meta分析的局限性包括:①仅纳入7个RCTs,没有绘制漏斗图,且纳入RCTs多为小样本临床试验,在一定程度上降低了本研究的质量和证据强度;②纳入RCTs在疗程、用药剂量、基础用药等方面有一定差异,研究间存在临床异质性问题;③Meta分析显示雷诺嗪不增加T2DM患者的低血糖风险,但置信区间较大,存在一定的偏倚,可能与样本量较小有关。因此,需要更多高质量、大样本、长期随访的RCTs进一步证实雷诺嗪对T2DM的安全性与有效性。

表2 雷诺嗪与对照组治疗T2DM患者的不良事件发生率(%)

| Tab.2 Incidence of adverse events for ranolazine compared with control (%) |
|---|---|---|---|---|---|---|
| 便秘 | 1.9/0.5 | 2.2/1.3 | - | 3.2/0 | 2.9/4.0 |
| 头晕 | 2.3/2.3 | 2.2/0.4 | 7.7/0 | 1.8/1.8 | 1.5/7.8/1.8 |
| 恶心 | 5.1/3.2 | - | 7.7/2.4 | 3.2/4.1 | 4.4/3.3/1.8 |
| 乏力 | - | - | 5.1/0 | - | 1.5/7.8/0 |
| 心绞痛 | - | 0.4/0.4 | - | - | 4.4/1.6/5.3 |
| 高血糖 | 1.9/1.9 | 2.6/0.9 | 2.6/7.3 | 0.9/2.3 | - |
| 乏力 | 9.8/14.8 | 8.2/9.9 | 2.6/12.2 | 8.2/6.3 | - |


