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Review Article

Safety of basal-bolus versus premixed insulin intensification regimens in the management of type 2 diabetes mellitus: A narrative review of a 14-year experience

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الملخص

أهداف البحث: لا يزال اختيار أفضل وصفة لإعطاء الإنسولين بغرض تكثيف العلاج في حالات داء السكري من النوع الثاني موضع جدل. على الرغم من كثرة البحوث، فإن الأدلة على النواحي الآمنة لتلك الوصفات لم يتم تلخيصها حتى الآن. قمنا بمراجعة سردية لمقارنة مخرجات الأمان بين وصفات الإنسولين متعدد الجرعات والوصفات المحتوية على الإنسولين مسبق الخلط.

طرق البحث: قمنا بالبحث في قواعد المعلومات الإلكترونية عن الدراسات المنشورة باللغة الإنجليزية بين يناير ٢٠٠٠م وديسمبر ٢٠١٤م، للتعرف على الدراسات التي أجريت للمقارنة بين الوصفات المختلفة لتكثيف الإنسولين. من بين تلك الدراسات، تم اختيار الدراسات التي تم فيها قياس المعايير المتعلقة بأمان تلك الوصفات عند البالغين الذين يعانين من داء السكري من النوع الثاني فقط للدراسة المرجعية. وتمت مراجعة المعلومات المستخلصة من قبل باحثين إثنين، وحلت اختلافات وجهات النظر بالمناقشة.

النتائج: من بين الـ ٢٠ دراسة التي درست، شمل البحث الـ١٠ دراسات التي قارنت بشكل خاص مؤشرات الأمان بين وصفات الإنسولين متعدد الجرعات، والوصفات المحتوية على الإنسولين مسبق الخلط. ومن بين مخرجات الأمان التي تم قياسها انخفاض سكر الدم، زيادة الوزن والأحداث السلبية. بشكل عام، وجدنا وصفة الإنسولين متعدد الجرعات مقاربة لوصفة الإنسولين مسبق الخلط في ما يتعلق بانخفاض سكر الدم والأحداث السلبية. أما بالنسبة لزيادة الوزن، فقد أظهرت دراستان من بين سبع دراسات زيادة وزن ذات قيمة في المجموعة المستخدمة لوصفة الإنسولين متعدد الجرعات.

الاستنتاجات: بشكل عام فإن ملف السلامة لوصفة الإنسولين متعدد الجرعات مقارب لوصفة الإنسولين مسبق الخلط. لم تقارن أي من الدراسات التي درست وصفات تكثيف الإنسولين في ذراعي الدراسة بصورة مباشرة. كما ينبغي إجراء الدراسات لمقارنة الإنسولين غير التناظري.

الكلمات المفتاحية: وصفات تكثيف الإنسولين؛ مسبق الخلط؛ الأمان؛ داء السكري من النوع الثاني

Abstract

Objectives: The best insulin regimen for the intensification of insulin therapy in the management of type 2 diabetes mellitus (T2DM) remains controversial. Despite substantial research, the body of evidence concerning the safety aspects of such regimens has never been summarized. We conducted a 14-year narrative review to compare the safety outcomes of basal-bolus (BB) versus premixed (PM) insulin regimens.

Methods: We searched electronic databases (PubMed, Scopus, Proquest and Google Scholar) for English-language studies published from January 2000 to December 2014 to identify studies comparing insulin intensification regimens. Only studies measuring the

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safety-related parameters of the specific regimens in T2DM adult patients were selected for further review. The extracted data were independently reviewed by two researchers, and disagreements were resolved by discussion.

Results: Of the 20 retrieved studies, we included 10 studies that specifically compared the safety parameters of BB and PM Insulin regimens. Among the safety outcomes measured were hypoglycaemia, weight gain and adverse events. Broadly, we determined that the BB insulin regimens were comparable to the PM insulin regimens in terms of hypoglycaemia and adverse events. In terms of weight gain, two of seven studies showed significant weight gain in BB insulin regimen arms.

Conclusions: Generally, the safety profile of BB insulin regimen was comparable to that of the PM insulin regimen. None of the identified studies performed head-to-head comparisons utilizing human insulin regimens in both arms. Research comparing non-analogue insulin regimens is warranted.

Keywords: Basal-bolus; Insulin intensification regimen; Premixed; Safety; Type 2 diabetes mellitus

Introduction

Diabetes mellitus is becoming one of the most highly problematic health concerns of the 21st Century.[1] Findings from United Kingdom Prospective Diabetes Study (UKPDS) revealed that affected Type 2 Diabetes mellitus (T2DM) patients usually lose half of their β-cell functions at the point of diagnosis, with a further annual decline of 5%.[2] Most people need to begin treatment with oral anti-diabetic agents combined with a lifestyle modification strategy. In reality, normal glycaemic control is difficult to achieve with lifestyle changes alone.

In T2DM patients, with time, oral anti-diabetic agents usually lose their effectiveness and patients need to seek exogenous insulin therapy. Generally, implementation of a successful insulin therapy requires three stages of treatment, including insulin initiation, optimization and intensification.[3] For insulin intensification, when glycaemia is not achieved after the initiation and optimization of insulin, numerous recommendations exist in various guidelines for the selection of a second-line insulin regimen.

Insulin therapy initiation with basal insulin or a premixed insulin regimen, has been recommended in several local and international practice guidelines as well as publications[3–8] However, for insulin intensification, when normoglycaemia is not achieved after insulin initiation, various intensification recommendations exist, although there is no clear strategy for the selection of the second-line insulin regimen.[9] Among the recommendations for insulin intensification, switching to an intensified premixed insulin regimen,[10–12] Basal-plus insulin regimen[13–15] or Basal-bolus insulin regimen[12,16,17] may be included.

Multiple meta-analyses have been performed with regards to insulin therapy comparisons. Lasserson et al., Giugliano et al. and Vaag et al. conducted a meta-analysis to compare and summarize the glucose control, clinical outcomes or adverse events occurring with the use of various individual insulin types, such as basal, biphasic and prandial insulin therapy.[6,18,19] Sumeet et al. otherwise performed a meta-analysis on studies comparing conventional insulin versus analogue insulin.[20] Four trials reviewed in the previous meta-analysis by Lasserson et al. (n = 3/22)[6] and Giugliano et al. (n = 2/16)[19] were included in our review because they met our review inclusion criteria.

To the best of our knowledge, there has been no published literature review specifically summarising the safety related outcomes of BB versus PM insulin intensification regimens. Thus, this review attempts to provide a comparative overview of safety related outcomes involving the two insulin intensification regimens.

Materials and Methods

We searched electronic databases (PubMed, Scopus, Proquest and Google Scholar) from January 2000 to December 2014 to identify studies comparing insulin intensification regimens. We searched for English Language papers published from 2000 to 2014 with the following terms: "INSULIN" AND "BASAL-BOLUS" or "PRANDIAL-BASAL" AND "PREMIXED" or "BIPHASIC" AND "COMPARISON" NOT "PAEDIATRIC." The main inclusion criteria were studies comparing BB regimens versus PM regimens alone in T2DM patients and measuring safety related parameters. Any studies involving paediatric patients were excluded. The data of each extracted safety parameter was also independently reviewed by other researchers. Disagreements during the data extraction were resolved by discussion between the researchers.

Results

Our initial search identified 20 papers,[12,21–39] five studies of which were excludes[21,24,32,38,39] because they compared regimens other than the two specific regimens, two were excluded because they involved Type 1 Diabetes Mellitus patients,[22,34] two were excluded because there was no safety related parameter measured in the study[31,35] and one was excluded due to different injection formulations used for the BB regimen arm.[37] The remaining ten selected studies and their characteristics were analysed as shown in Table 1.[12,23,25–30,33,36] The safety parameters measured within the studies were also analysed (Table 2).[12,23,25–30,33,36]

1. Hypoglycaemia

Most of the studies use different terminologies and definition for hypoglycaemia hypoglycaemia based on severity and time period classifications (Table 3).[12,23,25,27,28,30,33,36] Hypoglycaemia was defined by Rosenstock et al. as an