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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

Table 1: Characteristics of the selected studies.

Source	Study duration (Week)	Study sites	Number of study subjects, n	Study Arm 1	Study Arm 2
(Ligthelm et al., 2006)[28]	16	Multicentre (Germany, United Kingdom, France, Spain, Poland, the Netherlands, Sweden, Croatia, Romania, Russia, Hong Kong, Singapore and Malaysia)	394	Human isophane insulin (NPH) and insulin aspart (IAsp) thrice daily	Biphasic insulin aspart thrice daily meal-.BIAsp 70 (BMI $\leq$30) or BIAsp 50 (BMI>30) with breakfast and lunch and BIAsp 30 with dinner
(Rosenstock et al., 2008)[12]	24	Multicentre (United states and Puerto Rico)	374	Glargine at bedtime and mealtime lispro	Humalog Mix 50/50 thrice daily with meals. Humalog Mix 50/50 replaceable with Humalog Mix 75/25 at the evening meal if the fasting plasma glucose target unachievable
(Masuda et al., 2008)[29]	12	Single-centre study (Tokyo, Japan)	28	NPH insulin at bedtime and preprandial insulin lispro	Lispro Mix 50/50 twice daily
(Liebl et al., 2009)[27]	26	Multicentre (Austria, Germany and Switzerland)	719	Insulin detemir once daily and insulin aspart mealtimes	Biphasic insulin aspart (30/70) twice daily
(Sakamoto et al., 2010)[33]	8	Single-centre study (Tokyo, Japan)	37	NPH insulin at bedtime and preprandial insulin lispro or insulin aspart.	Twice daily of 50/50 premixed insulin lispro or 30/70 premixed insulin aspart.
(Fritsche, Larbig, Owens, & Häring, 2010)[23]	52	Multicentre (Europe and Australia)	310	Insulin glargine and premeal glulisine	Biphasic human insulin (30/70) or BIAsp 70/30 twice daily
(Miser et al., 2010)[30]	24	Multicentre (Argentina, Australia, Brazil, Canada, Greece, Iran, India, Netherlands, Romania, Spain, and United States.)	399 (intensification arm A), 345 (intensification arm B)	Glargine insulin once daily and mealtime insulin lispro thrice daily	Lispro Mix 50/50 thrice daily or Lispro Mix 75/25 twice daily
(Levin et al., 2011)[26]	36	Multicentre (United States)	197	Insulin glargine and premeal glulisine	Lispro mix 75/25 or Biasp 70/30 (frequency undefined)
(Hsia et al., 2011)[25]	<1	Single-centre study (Colorado, United States)	22	Glargine insulin once daily and mealtime insulin lispro thrice daily	Biphasic human insulin (30/70) twice daily or thrice daily
(Walia, Upreti, Bhansali, Dutta, & Shanmugasundar, 2012)[36]	12	Single-centre study (Chandigarh, India)	50	Basal detemir once or twice daily and bolus aspart	Biphasic human insulin (30/70) thrice daily

Table 2: Safety parameters measured from the selected studies.

No.	Source	Safety parameters measured		
		Hypoglycaemia	Weight Gain	Adverse Events
1	(Ligthelm et al., 2006)[28]	•	•	•
2	(Rosenstock et al., 2008)[12]	•	•	•
3	(Masuda et al., 2008)[29]	•		
4	(Liebl et al., 2009)[27]	•	•	
5	(Sakamoto et al., 2010)[33]	•		
6	(Fritsche et al., 2010)[23]	•	•	•
7	(Miser et al., 2010)[30]	•	•	•
8	(Levin et al., 2011)[26]	•	•	
9	(Hsia et al., 2011)[25]	•		
10	(Walia, Upreti, Bhansali, Dutta, & Shanmugasundar, 2012)[36]	•	•	•

episode with classic cognitive and/or adrenergic signs that is confirmed with or without the plasma glucose (PG) levels.[12] However, Miser et al. and Hsia et al. defined hypoglycaemia as having a PG level of ≤70 mg/dL (3.9 mmol/l) or experiencing symptoms typically related with hypoglycaemia.[25,30] All ten selected studies assessed hypoglycaemia as a safety comparison parameter.[12,23,25–30,33,36] In all of the studies, there was no statistical significant difference in terms of the number or proportion (percentage) of subjects experiencing hypoglycaemia episodes, number of hypoglycaemic episodes and incidence rate of hypoglycaemia (events/subject/week) between patients who were on the BB or PM regimen (Table 4).[12,23,25–30,33,36] However, a sub-hoc analysis of the total minor hypoglycaemia events in one of the studies by Walia et al. showed a significantly higher number of documented symptomatic hypoglycaemic episodes in the BB regimen arm.[36]

2. *Weight gain*

A change in weight from the baseline to the endpoint was measured in seven out of ten studies analysed. All seven studies showed that there was an increase in weight in both groups (Table 5).[12,23,26–28,30,36] Two out of seven studies showed that the BB arm showed statistically significant weight gain compared to the PM arm,[23,26] while the remaining five studies indicated that the increase was comparable across arms.[12,27,28,30,36]

Table 3: Classification of the hypoglycaemia terms from the selected studies.

Classification factor	Term used		Definitions
Severity	Self-treatable (Minor)	Asymptomatic	•No symptoms of hypoglycaemia but PG level ≤70 mg/dl (3.9 mmol/l)[36] •Among minor hypoglycaemia subcategorization:- asymptomatic hypoglycaemia[36]
		Symptomatic	• Symptoms of hypoglycaemia based on plasma glucose levels either ≤72 mg/dl (4 mmol/l)[12] ≤70 mg/dl (3.9 mmol/l)[25,30], ≤60 mg/dl (3.3 mmol/l)[12] or ≥56 mg/dl (≥3.1 mmol/L)[28] <56 mg/dl (<3.1 mmol/L)[27,28] ≤50 mg/dl (2.8 mmol/l)[12,33] • Not requiring assistance by another individual. • Among minor hypoglycaemia subcategorization:- documented symptomatic hypoglycaemia, probable symptomatic hypoglycaemia and relative hypoglycaemia[36]
	Self-untreatable (Major or Severe)		• Associated with plasma glucose level of <36 mg/dl (2.0 mmol/l) and patient require third-party help, including oral carbohydrate, i.v. glucose or i.m. glucagon.[12,23,27,28,30,33]
Time periods	Nocturnal		• Episodes occurring between 00:00 and 06:00, inclusive of both times[28] • Episodes occurring between 22:00 and 06:00, inclusive of both times[36] • Episodes occurring after bedtime and before the morning meal or insulin dose[30]
	Daytime		• Episodes occurring outside the 00:00 and 06:00 time interval[28]

3. Adverse events

Adverse events are defined as any unfavourable and unintentional sign, symptom, syndrome or illness that occurs or worsens during the study.[23] However, Serious Adverse Events (SAEs) is defined as an occurrence at any dose, resulting in mortality, persistent or significant incapability, congenital defect, life-harming experience, hospitalization,

Table 4: Hypoglycaemia related findings from the selected studies.

Hypoglycaemic terms	Variable	Source	BB Arm	PM Arm	*p*-Value*
Minor	Number and percentage of subjects experiencing hypoglycaemic episodes, N (%)	(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	15 (44.0)	20 (80.0)	n.a
		(Fritsche et al., 2010)[23]	106(69.3)	101 (64.3)	0.298
		(Rosenstock et al., 2008)[12,a]	165 (88.2)	165 (88.2)	1.000
		(Levin et al., 2011)[26]	n.a (36.0)	n.a (42.0)	0.370
	Number of hypoglycaemic episodes, E	(Fritsche et al., 2010)[23]	1369	1987	n.a
		(Hsia et al., 2011)[25,b]	5	3	0.050
		(Liebl et al., 2009)[27]	11	0	n.a
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	37	53	n.a
	Incidence rate, (events/subject/week)	(Fritsche et al., 2010)[23]	0.19	0.26	0.236
		(Rosenstock et al., 2008)[12,a]	0.86	0.89	0.747
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	0.12	0.18	n.a
		(Liebl et al., 2009)[27]	0.04	0.04	0.837
		(Masuda et al., 2008)[29,c,d]	0.32	0.26	n.s
Major	Number and percentage of subjects experiencing hypoglycaemic episodes, N (%)	(Ligthelm et al., 2006)[28]	2 (1.0)	6 (3.1)	n.s
		(Rosenstock et al., 2008)[12]	4 (2.1)	6(3.2)	0.751
		(Fritsche et al., 2010)[23]	12(7.8)	12(7.6)	0.946
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	3(12.0)	2(8.0)	0.520
		(Miser et al., 2010)[30,e]	n.a (0)	n.a(1.0)	0.166
		(Miser et al., 2010)[30,f]	n.a (0)	n.a(1.0)	0.188
		(Liebl et al., 2009)[27]	n.a (0.9)	n.a (0)	n.a
	Number of hypoglycaemic episodes, E	(Miser et al., 2010)[30,e]	0	2	0.166
		(Miser et al., 2010)[30,f]	0	2	0.188
		(Ligthelm et al., 2006)[28]	2	7	n.s
		(Fritsche et al., 2010)[23]	18	30	n.a
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	3	2	n.a
		(Sakamoto et al., 2010)[33]	0	0	n.a
	Incidence Rate, (events/subject/week)	(Rosenstock et al., 2008)[12]	0.001	0.002	0.266
		(Fritsche et al., 2010)[23]	0.002	0.004	0.234
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	0.010	0.010	n.a
Nocturnal	Number and percentage of subjects experiencing hypoglycaemic episodes, N (%)	(Liebl et al., 2009)[27]	40 (7.4)	13(7.3)	n.s
		(Rosenstock et al., 2008)[12]	110 (58.8)	109 (58.2)	1.000
		(Fritsche et al., 2010)[23]	60 (39.2)	68 (43.3)	0.477
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	8 (32.0)	12(48.0)	n.a
	Number of hypoglycaemic episodes, E	(Fritsche et al., 2010)[23]	281	329	n.a
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	13	15	n.a
	Incidence Rate, (events/subject/week)	(Rosenstock et al., 2008)[12,c]	0.120	0.090	0.139
		(Fritsche et al., 2010)[23]	0.040	0.050	0.966
		(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	0.040	0.050	n.a
		(Miser et al., 2010)[30,e]	0.060	0.050	0.657
		(Miser et al., 2010)[30,f]	0.050	0.050	0.949

n.a: not available in the literature; **n.s:** not statistically significant. The data presented in this table were extracted from the articles as reported by the original authors. * A *p* value of <0.05 was chosen as the level of significance.

[a] Findings based on PG level $<$ 72 mg/dl (4 mmol/l).

[b] Findings based on PG level $<$ 70 mg/dl (3.9 mmol/l).

[c] Converted from literature to Incidence Rate, (events/subject/week).

[d] Assumed symptomatic hypoglycaemia as not specified in the literature.

[e] Arm A: premixed regimen used is Lispro Mix 75/25 BID.

[f] Arm B: premixed regimen used is LM50/50 TID.

Table 5: Summary of weight change findings from the selected studies.

Source	Mean weight changes, kg[a]		*p-Value
	PM regimen	BB regimen	
(Rosenstock et al., 2008)[12]	4.0 ± 4.2	4.5 ± 4.4	0.22
(Liebl et al., 2009)[27]	2.1 ± 4.0	2.4 ± 4.1	>0.05
(Miser et al., 2010)[30]	0.9 ± 3.4[b]	1.4 ± 3.0[b]	0.10
	0.9 ± 3.5[c]	0.6 ± 2.9[c]	0.35
(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	1.5 ± 0.3[d]	1.4 ± 0.3[d]	>0.05
(Ligthelm et al., 2006)[28]	2.0[e]	2.0[e]	>0.05
(Levin et al., 2011)[26]	6.3(13.9 lbs) [e,f]	3.1(6.9 lbs)[e,f]	*0.03*
(Fritsche et al., 2010)[23]	3.6 ± 4.0	2.2 ± 4.5	*0.01*

The data presented in the table were extracted from the articles as reported by the original authors. * A p value of <0.05 was chosen as the level of significance.

[a] Data were reported as the mean ± s.d, unless otherwise specified.
[b] Arm A: premixed regimen used is Lispro Mix 75/25 BID.
[c] Arm B: premixed regimen used is LM50/50 TID.
[d] Data reported as the mean ± Standard Error of the Mean (SEM).
[e] Data for the standard deviation not available.
[f] Data converted from lbs to kg, conversion Rate 1 kg = 2.2 lbs.

prolongation of hospitalization or any other event deemed serious by the researcher.[23,30] Five studies reported an incidence of adverse events while on the insulin regimens.[12,23,28,30,36] The incidence of adverse events was also evaluated via observation by the investigators or reports by the patients at each point of investigator-patient contact.[23,28]

Adverse events reported in the literature were categorized into three categories: overall, mild or serious (Table 6).[12,23,28,30,36] In terms of the overall adverse events, Lighthelm et al. documented that the most frequent adverse events were headache, rhinopharyngitis and hypertension.[28] In addition, Rosenstock et al. reported that one BB arm patient had to be withdrawn from the study due to oedema, shortness of breath and elevated creatinine levels.[12] In terms of SAEs, Rosenstock et al. reported that one patient each from the PM and BB arm had to be withdrawn from the study due to acute respiratory failure and myocardial infarction, respectively.[12] All five studies demonstrated that there was no statistical significant difference between the PM and BB arm in terms of adverse events.[12,23,28,30,36]

Mortality was also reported in the studies as one of the SAEs. In one of the studies, there was one death reported that was unrelated to the trial product in which an elderly patient died seven days post-PM regimen initiation due to myocardial infarction.[28] However, another study reported two deaths overall, one in each arm, which were both unrelated to the trial product; the cause of death not described in the literature.[23] Furthermore, one death in the BB arm caused by cardiovascular related SAEs was reported in another study.[30]

Discussion

This review observed that the key safety parameters measured in previous comparative studies on the safety of different insulin intensification regimens included hypoglycaemia, weight gain and adverse events.

Our review observed that hypoglycaemia was defined differently using specific terminologies in the selected studies.[12,23,25,27,28,30,33,36] Moreover, we found that all ten studies reported no statistical significant difference in terms of hypoglycaemia related measurements, such as the number of subjects experiencing hypoglycaemia episodes, hypoglycaemic episodes and incidence rate of hypoglycaemia in patients utilizing either the BB or PM insulin regimen.[12,23,25–30,33,36] However, a study by Walia et al. further examined and categorized the incidence of hypoglycaemia into major and minor hypoglycaemia. Minor hypoglycaemia was further sub-divided into four subcategories: documented symptomatic hypoglycaemia, probable symptomatic hypoglycaemia, asymptomatic hypoglycaemia and relative hypoglycaemia. A sub-hoc analysis of the minor hypoglycaemia events in this study showed a statistically significantly number of documented symptomatic hypoglycaemic episodes in the BB regimen arm compared to the PM regimen arm.[36] The general finding from our review lends support to two previous meta-analyses that demonstrated that the overall rate or incidence of hypoglycaemia among the two different regimens was comparable.[6,19]

Excessive weight gain may result in cardiovascular complications, and via psychological barriers and adherence hindering effects, it may lead to an increased risk of diabetic morbidity and mortality.[40] Two out of seven studies showed that the BB arm had a statistically significant weight gain compared to the PM arm,[24,27] while the remaining five studies showed that the increase was comparable across arms.[12,27,28,30,36] The reason for this discrepancy is unclear, but it may be due to the relatively smaller sample size and partly due to the use of only a twice daily premixed insulin regimen in these two studies and not a thrice daily regimen as described in the other analysed studies. Fritsche et al. further demonstrated that weight gain across the arm may not be considered clinically significant, although there was statistically significant difference in weight gained among their study population, as this increment was within the normal range for weight

Table 6: Adverse events data from the selected studies.

Category	Study	Adverse events					
		Overall		Mild		Serious	
		BB	PM	BB	PM	BB	PM
Number of patients, n (%), Number of Events [n]	(Ligthelm et al., 2006)[28]	110 (55.6%), [290]	110 (56.1%), [253]	[253]	[223]	9 [10]	7 [8]
	(Fritsche et al., 2010)[23]	90 (58.8%), [328]	95 (60.5%), [371]			26	24
	(Miser et al., 2010)[30,a]					20	15
	(Walia, Upreti, Bhansali, Dutta, Shanmugasundar, et al., 2012)[36]	26[53][c]	34[70][c]			3[b]	2[b]
	(Rosenstock et al., 2008)[12]					[13]	[9]
No of events unrelated to trial Product[n]	(Ligthelm et al., 2006)[28]	[190]	[175]			[8]	[6]
	(Rosenstock et al., 2008)[12]					[12]	[9]
No. of patient withdrawals due to adverse event, n	(Ligthelm et al., 2006)[28]	3	4				
	(Fritsche et al., 2010)[23]	7	3				
	(Miser et al., 2010)[30,a]	4	4				
	(Rosenstock et al., 2008)[12]			1	0	1	1
No. of adverse events by the organ system, [n]:	(Fritsche et al., 2010)[23]					[5]	[7]
	(Miser et al., 2010)[30,a]					[11]	[7]
• Cardiovascular event							
• Nervous system disorders	(Fritsche et al., 2010)[23]					[2]	[0]
• Metabolism and nutrition disorders or Endocrine	(Fritsche et al., 2010)[23]					[4]	[1]
	(Miser et al., 2010)[30,a]					[1]	[1]
• Other	(Fritsche et al., 2010)[23]					[18]	[23]
	(Miser et al., 2010)[30,a]					[20]	[7]

The data presented in the table were extracted from the articles as reported by the original authors.
Shaded area indicates data not available from the literature.
[a] Combined total of both Intensification Arm A&B.
[b] Data based on the occurrence of major hypoglycaemia.
[c] Data based on overall hypoglycaemia (minor, major and nocturnal).

maintenance, defined as a weight change of less than 3% of body weight.[23,41]

The next safety parameter of concern is adverse events. In our review, we found only two studies defined adverse events and SAEs.[23,30] Five studies measured this parameter, although none of the studies showed any statistical significant difference between the BB and PM arms. The findings from our review were consistent with those reported by previous meta-analyses, which concluded that the incidence of adverse events, such as severe hypoglycaemia or general hypoglycaemia were similar across the two insulin arms.[6,19] Four trials reviewed in the two previous meta-analysis by Lasserson et al. (n = 3/22)[12,28,31] and Giugliano et al. (n = 2/16)[12,27] were included in our review because they met our review inclusion criteria. Various adverse events and serious adverse events were reported in the studies analysed. This narrative review and previous meta-analysis together highlights that incidence of hypoglycaemia is a serious adverse event of insulin therapy and consideration must be taken when selecting different types of insulin regimens.

From this 14-year literature review analysis, we found that none of the studies compared safety parameters for the non-analogue insulin regimen in both arms. All of the studies found thus far have at least one analogue component in at least one of its arms. In developing countries, the use of analogue insulin, rapid or long-acting in comparison to human insulin, is very low, because cost is a concern in the public healthcare setting.[7,42] Thus, because human insulin is still the mainstay of therapy in developing countries, conducting future insulin comparative studies utilizing human insulin regimens is crucial to measure for any differences in the findings.

Limitations

Nevertheless, this review has some limitations. The studies included in this review were all in the English language, and thus, some studies in other languages may have been missed. In addition, in this review, each individual study has its varied inclusion and exclusion criteria as well as different dosing and frequencies of insulin utilized in each study arm.

Conclusion

Our review on the safety comparison of insulin intensification regimens indicated that the BB and PM insulin regimens are equally safe in terms of the rate of hypoglycaemia and adverse events. Only weight gain was observed to have a statistically significant difference among patients in the BB

arm in two of the studies. Thus, our review concluded that the BB and PM regimens are comparably safe for use in T2DM patients. Moreover, we found that all of the studies in our review involved analogue insulin regimens. Previous studies have shown that human insulin is still highly utilized in public healthcare settings in developing countries due to its relatively lower cost compared to analogue insulins. Thus, further research comparing these two intensification regimens, but using human insulin, warrants future analysis to measure any difference in the findings.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

1. NIP designed the study with input from NO, NMN and FNN. NIP reviewed the journals and identified the safety related parameters. NO and NMN independently reviewed the extracted data. NIP obtained and interpreted the data and drafted the manuscript. NIP, NO, NMN and FNN were responsible for critical revision of the manuscript and approved the final version submitted. 2. NIP, NO, NMN and FNN agreed with the manuscript's results and conclusions. NIP, NO, NMN and FNN contributed to the writing of the paper.

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