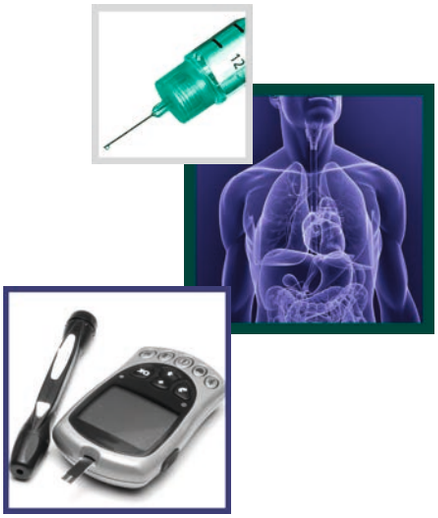
RESEARCH ARTICLE

Intravenous insulin aspart in a hospital setting: results from an observational study examining patient outcomes and physician preferences



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Summary Points

- Hyperglycemia occurs commonly in critically ill individuals, even those with no history of diabetes, and can cause adverse clinical outcomes.
- Intravenous (iv.) insulin therapy is recommended for the control of hyperglycemia in critically ill patients in the hospital setting because the short half-life of insulin following iv. delivery allows rapid dosing adjustments to be made.
- Once the illness is less critical and the patient begins eating regular meals, they should be transitioned to subcutaneous insulin.
- There are no available data on the use of iv. insulin aspart (IAsp) for the management of inpatient hyperglycemia.
- Intravenous IAsp effectively reduced mean blood glucose in the overall patient population and in those patients treated in the intensive care unit (ICU) and non-ICU settings.
- Serious adverse events were reported in six patients (0.2%), but none were considered to be related to treatment.
- Rates of major and minor hypoglycemia were 0.6 and 2.8%, respectively.
- Based on these data, iv. IAsp appears to be an effective and well-tolerated option for managing inpatient hyperglycemia in ICU and non-ICU settings.

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SUMMARY **Aims:** Clinical data on the use of intravenous (iv.) insulin aspart (IAsp) for the management of inpatient hyperglycemia are limited. This study evaluated the safety and efficacy of iv. IAsp in normal clinical practice in India. **Materials & methods:** This was an open-label, nonrandomized, noninterventional, observational study of 3024 hospitalized subjects (67% intensive care unit [ICU] and 33% non-ICU) requiring iv. insulin. The decision to initiate iv. IAsp and decisions on dose/dosing frequency were made by the physician. Glucose testing was carried out according to local protocol in each center. The primary objective was to evaluate the incidence and type of adverse events/serious adverse events during therapy. Secondary objectives included physician-reported mean blood glucose (BG) measurements, duration of iv. treatment and total insulin dose, BG 24 h after transferring to subcutaneous (sc.) therapy, number of hypoglycemic events, mortality and ease of transferring from iv. to sc. administration. **Results:** iv. IAsp reduced the mean BG from 19.8 mmol/l at treatment start to 8.6 mmol/l at treatment end. Similar results were observed in ICU (20.7–8.4 mmol/l; p = 0.0001) and non-ICU (17.7–8.9 mmol/l; p = 0.0001) settings. Serious adverse events were reported in six patients (0.2%), none were considered to be related to study medication. Rates of major and minor hypoglycemia were 0.6 and 2.8%, respectively. Most physicians (98.6%) expressed a preference to use IAsp in the future owing to rapid achievement of target BG, positive safety profile and convenience of shifting from iv. to sc. administration. **Conclusion:** iv. IAsp is an effective and well-tolerated option for managing inpatient hyperglycemia in ICU and non-ICU settings.

Hyperglycemia occurs commonly in critically ill individuals, even for those with no history of diabetes, and it is a known risk factor for adverse outcomes [1,2]. For example, in a population consisting of diabetic (n = 396) and nondiabetic (n = 753) individuals with acute coronary syndrome divided into groups according to the quartiles of hyperglycemia at admission, higher levels of hyperglycemia at admission were associated with higher in-hospital, 30-day and 3-year mortalities [3]. When these subgroups were analyzed independently there were no significant differences in mortality with increasing glycemia in individuals with diabetes. By contrast, in nondiabetic individuals, higher hyperglycemia at admission was associated with increased in-hospital and 3-year mortality [3]. In the intensive care unit (ICU) setting, hyperglycemia was associated with a significantly increased mortality in individuals without diabetes, but not in those with diabetes [4]. In the non-ICU setting, there is evidence for an association between hyperglycemia and poor clinical outcomes, including prolonged length of hospital stay, infection, disability after discharge from the hospital and increased mortality [2].

Intravenous (iv.) insulin therapy is recommended for the control of hyperglycemia in critically ill patients with or without diabetes in the hospital setting because of its short half-life following iv. delivery, which allows rapid dosing adjustments to be made [2,5]. In addition, the iv. route may be preferable to the subcutaneous (sc.) route in critically ill individuals because insulin absorption following sc. injection may be impaired owing to factors including peripheral edema and reduced perfusion of sc. sites [6]. Once an individual's illness is less critical and they begin eating regular meals, they should be transitioned to sc. insulin [2].

Although there is clear evidence that hyperglycemia has adverse consequences in critically ill individuals, there are conflicting data on appropriate glycemic targets in such patients. In one study, intensive iv. insulin therapy with the aim of maintaining blood glucose (BG) values within the target range of 80–110 mg/dl (4.4–6.1 mmol/l) improved morbidity and reduced mortality rates compared with maintenance of BG within a target range of 180–200 mg/dl (10–11.1 mmol/l) [7]. However, other studies have not shown as clear a benefit, and in some cases such stringent glucose targets have resulted in increased mortality [8,9]. Therefore, current guidelines recommend a target range of 140–180 mg/dl (7.8–10.0 mmol/l) in critically ill individuals, with the advice that benefits may be achieved by targeting the lower end of this range [2]. For noncritically ill inpatients, a pre-meal glucose target of <140 mg/dl (<7.8 mmol/l) and random BG target of <180 mg/dl (<10.0 mmol/l) are recommended [2]. Lower glucose targets (110–140 mg/dl; 6.1–7.8 mmol/l) may be appropriate in some patients, if they can be achieved without significant hypoglycemia [5].

Insulin aspart (IAsp; NovoRapid®, Novo Nordisk A/S, Bagsvaerd, Denmark) is a

rapid-acting insulin analog with efficacy and safety benefits compared with short-acting regular human insulin [10,11]. IAsp is approved for sc. use with a pen injection device, via an insulin pump or as an iv. infusion in a number of countries/regions, including India, Europe and the USA [10,12,13]. Clinical data on the use of iv. IAsp for the management of inpatient hyperglycemia are limited. Therefore, the objective of this study was to evaluate the safety and efficacy of iv. IAsp in routine clinical practice in India.

Methods

Study design

This was an open-label, nonrandomized, noninterventional, observational study of 3024 hospitalized subjects requiring iv. insulin. Subjects were enrolled from 136 trial sites across India between 16 March and 15 September 2008. The decision to prescribe iv. IAsp was made solely by the treating physician, based on their clinical evaluation. The treating physician determined the starting dose and frequency, as well as any later changes to either dose or frequency of iv. IAsp treatment. Owing to the fact that this is an observational study, glucose testing was carried out according to local protocol in each center. IAsp was commercially available and no financial support was provided to subjects. No comparator treatment arm was included in this study. The trial was conducted in accordance with the Declaration of Helsinki [101] and the Guidelines for Good Pharmacoepidemiology Practices [102]. This study was approved by an Independent Ethics Committee. The Independent Ethics Committee reviewed and approved all study-related documents. All subjects provided study-specific verbal informed consent before entry to the study.

Inclusion & exclusion criteria

Any hospitalized subject requiring iv. insulin therapy was eligible for the study. Subjects were excluded from the study if they were judged unlikely to comply with the protocol (e.g., uncooperative attitude, if they had hypersensitivity to IAsp or to any of the excipients, or if they had a condition that was contraindicated in the packaging insert).

Withdrawal

Subjects could withdraw at will at any time. The stopping of iv. insulin therapy was at the physician's discretion and was based upon their clinical evaluation.

Efficacy & safety end points

Before initiating iv. IAsp therapy, the following information was recorded: date of birth, gender, weight, height, medical history, date of admission to hospital/ICU, current diabetes medications (if any), most recent plasma glucose value, reason for initiating iv. IAsp and date started. During iv. IAsp therapy, the following information was recorded from hospital charts: BG measurements (measurements spread over 24 h), timing and dose of iv. IAsp, number and type of adverse events (AEs) and serious adverse events (SAEs), number of minor and major hypoglycemic episodes, number of rescue dextrose infusions/time that iv. IAsp was stopped due to hypoglycemia and clinical condition, and laboratory parameters of subjects. The following information was recorded 24 h after the cessation of iv. IAsp: BG measurements (at least ten, including one at the end of 24 h following cessation of iv. IAsp), timing and dose of substituted sc. insulin preparation, other medications administered, number of minor and major hypoglycemic episodes, and number and type of AEs and SAEs. Major hypoglycemia was defined as symptoms of hypoglycemia that the subject was unable to treat themselves and either: BG <2.2 mmol/l (<40 mg/dl); or reversal of symptoms after carbohydrate intake, glucagon or iv. glucose administration. Minor hypoglycemia was defined as either: symptoms of hypoglycemia with confirmation by BG of 2.2–3.8 mmol/l (40–69 mg/dl) and which is handled by the subject themselves; or any asymptomatic BG of 2.2–3.8 mmol/l (40–69 mg/dl). In addition, the treating physician entered comments on iv. IAsp in a questionnaire provided by the sponsor.

Objectives

Clinical data on the use of iv. IAsp for the management of inpatient hyperglycemia are limited. This study evaluated the safety and efficacy of iv. IAsp in normal clinical practice in India. The primary objective of this study was to evaluate the incidence and type of AEs and SAEs during iv. IAsp therapy. The secondary objectives were to evaluate: mean BG measurements during iv. IAsp treatment and at the end of treatment based on measurements recorded over 24 h; duration (hours) of iv. treatment and total dose (units) of insulin administered; BG levels 24 h after transferring to sc. therapy; number of minor and major hypoglycemic events and the requirement for rescue dextrose administration; mortality;

and ease of transferring from iv. infusion to sc. injection based on physician questionnaire.

Sample size

The primary objective of this study was to evaluate the safety of iv. IAsp. To provide a 95% probability of detecting SAEs with an incidence of at least 0.1%, a sample size of 3000 subjects was required.

Statistical methods

Demographic characteristics and hypoglycemic episodes were summarized with descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. The number of SAEs and AEs, and the number and percentage of subjects with AEs classified by system organ class and preferred term, were summarized. In addition, summary tables were prepared for SAEs and AEs by intensity and drug relationship.

Parametric inferential analyses were conducted for continuous variables with normal distribution, particularly those involving a comparison of means across two samples with a sample size of more than 30. Comparison of means across more than two samples simultaneously was performed with parametric inferential analyses based on the F distribution. Categorical variables were analyzed with nonparametric inferential analyses using χ^2 distribution. Statistical analyses were performed as two-sided tests and comparisons were considered statistically significant when $p \leq 0.05$. All statistical analyses were carried out 'R' software version 2.9.2 (2009).

Table 1. Demographics and baseline characteristics of the overall population.

Parameter	n	Proportion (%)	Parameter information missing, n (%)
Setting			
ICU	2010	67.3	38 (1.3)
Non-ICU	976	32.7	
Gender			
Male	1891	62.9	18 (0.6)
Female	1115	37.1	
Diabetes status			
Known diabetic	2557	86.2	59 (2.0)
Nondiabetic	408	13.8	
Baseline characteristics			
Mean weight: 69.7 kg	2877	–	147
Mean age: 53.5 years old	2272	–	752
Mean most recent A1C: 9.44%	1891	–	1133

A1C: Glycated hemoglobin; ICU: Intensive care unit.

Results

The safety analysis set included all subjects who received iv. IAsp and the efficacy analysis set included all subjects who had at least one measurement of BG, IAsp dose, hypoglycemic episodes or data on physician opinion after initiating iv. IAsp. All 3024 subjects had at least one criterion (baseline or post-baseline) to satisfy their inclusion in the safety analysis set and efficacy analysis set populations.

The majority of individuals (86.2%) included in the study had diabetes (Table 1). The mean ± SD age of patients was 53.5 ± 12.9 years and 62.9% were male. At baseline, mean ± SD of the most recent BG measurement was 18.9 ± 7.3 mmol/l and mean glycated hemoglobin was 9.4 ± 5.3.

A total of 67.3% of patients were admitted to an ICU setting and the remainder to a non-ICU setting (Table 1). There was no significant difference in mean age between ICU and non-ICU patients (53.8 years and 52.9 years; p = 0.09). Patients admitted to ICU had significantly higher mean most recent BG than those admitted to non-ICU units (19.8 mmol/l and 17.1 mmol/l, respectively; p = 0.0001). Mean glycated hemoglobin did not differ significantly in ICU (9.4%) and non-ICU (9.5%) patients (p = 0.94).

The majority of individuals received iv. IAsp for a metabolic disorder such as diabetic ketoacidosis (DKA) or uncontrolled hyperglycemia (69%). iv. IAsp was also administered to address hyperglycemia as part of perioperative care (10%); and for patients with hyperglycemia following admission for a range of conditions including cardiac disorders (6%), skin and soft tissue infections (4%), neurological disorders (3%), blood and lymphatic system disorders (2%), respiratory disorders (2%), gastrointestinal disorders (2%), infectious disease (1%) and miscellaneous (1%).

Insulin was administered by iv. bolus injection in 1277 cases (42.8%), via an infusion pump in 1087 cases (36.4%) and by microdrip in 626 cases (21.0%). The majority of patients in the ICU received insulin via an infusion pump (41.6%), whereas iv. bolus injection (54.2%) was the most common administration technique in non-ICU patients.

Six SAEs were reported in six subjects (0.2%): death due to septicemia and shock (n = 3), death due to myocardial infarction (n = 2) and death due to bleeding peptic ulcer (n = 1). All were assessed as unlikely to be related

to insulin treatment. At least one episode of major or minor hypoglycemia was experienced by 0.6 and 2.8% of patients, respectively (Table 2).

Treatment with iv. IAsp reduced mean ± SD BG from 19.8 ± 6.9 mmol/l at treatment start to 8.6 ± 2.9 mmol/l at treatment end. In patients in ICU and non-ICU settings, iv. IAsp significantly reduced mean BG from 20.7 to 8.4 mmol/l and from 17.7 to 8.9 mmol/l, respectively (p = 0.0001; Figure 1).

Median treatment duration and dose of iv. IAsp were 26 h and 80 units, respectively. Median IAsp dose was significantly higher in the ICU versus non-ICU setting (82 and 66 units, respectively; p = 0.0001). The most commonly used dilution fluid for iv. IAsp was normal saline in both the ICU (59.3%) and the non-ICU setting (69.1%). The other commonly used fluid was 5% dextrose.

In the majority of cases, subjects on iv. IAsp were transitioned to sc. treatment with IAsp (51.1%), biphasic IAsp (14.2%), biphasic human insulin (14.2%), or human soluble insulin (11.2%). A small number of subjects (9.4%) were shifted to other sc. insulins. Mean BG 24 hs after cessation of iv. IAsp was 8.2 mmol/l in the overall patient population. Mean BG after cessation of iv. IAsp was comparable in patients from ICU and non-ICU settings (8.3 mmol/l and 8.1 mmol/l, respectively; p = 0.07). Mean BG values were comparable 24 h after patients transferred from iv. IAsp to sc. treatment with IAsp (8.4 mmol/l), biphasic IAsp (8.1 mmol/l), human soluble insulin (8.0 mmol/l), human premix insulin (8.1 mmol/l) or other insulin (8.2 mmol/l).

Based on questionnaire responses, the majority of physicians (99%) expressed a preference to use IAsp in the future (Table 3). Those physicians who preferred IAsp were then questioned about the reasons for their preference with the following options: rapid achievement of target BG, its safety profile, convenience of shifting from iv. to sc. administration and other. Rapid achievement of target BG was the most common reason for physicians to prefer IAsp, followed by its safety profile and convenience of shifting from iv. to sc. administration (Table 4).

Discussion

iv. IAsp appears to be an effective and well-tolerated option for managing inpatient hyperglycemia in ICU as well as non-ICU settings. At the end of iv. IAsp treatment, the median duration of which was 26 h, mean BG values had fallen to between 8.4 and 8.9 mmol/l in the ICU, non-ICU and overall patient populations. These values are within the targets recommended by The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) for inpatient glycemic control of 7.8–10 mmol/l in critically ill individuals [2] and approach the predefined target BG range for the majority of clinicians of 5.6–8.3 mmol/l. By 24 h after cessation of iv. IAsp, these values had dropped further to between 8.1 and 8.3 mmol/l in non-ICU and ICU settings, respectively, which was still within the target range recommended by ADA/AACE [2] and the predefined target of clinicians. Fatal SAEs

Table 2. Patients experiencing at least one episode of hypoglycemia during intravenous insulin aspart therapy.

	ICU (n = 2010)	Non-ICU (n = 976)	Overall (n = 3024)
Major hypoglycemia† n (%)	14 (0.7)	3 (0.3)	17 (0.6)
Minor hypoglycemia‡ n (%)	61 (3.0)	24 (2.4)	85 (2.8)
Overall n (%)	75 (3.7)	27 (2.8)	102 (3.4)

†Major hypoglycemia defined as: symptoms of hypoglycemia that subject is unable to treat themselves and either blood glucose <2.2 mmol/l (<40 mg/dl); or reversal of symptoms after either carbohydrate intake, glucagon or intravenous glucose administration.
‡Minor hypoglycemia defined as either: symptoms of hypoglycemia with confirmation by blood glucose 2.2–3.8 mmol/l (40–69 mg/dl) and which is handled by the subject themselves; or any asymptomatic blood glucose 2.2–3.8 mmol/l (40–69 mg/dl).
ICU: Intensive care unit.

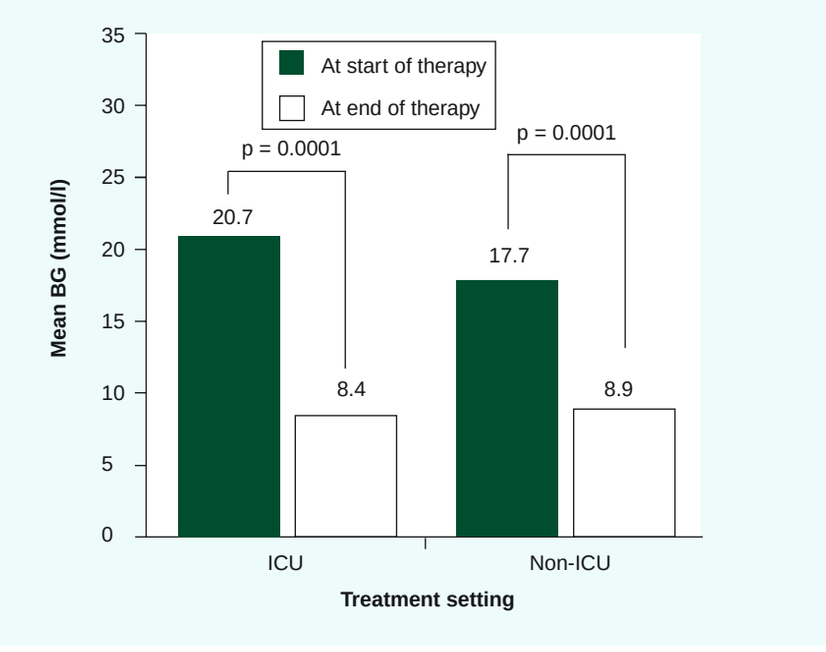

Figure 1. Blood glucose improvement with insulin aspart.
BG: Blood glucose; ICU: Intensive care unit.

were reported in six patients (0.2%) but none were thought to be related to study medication. The low mortality rate may reflect the fact that approximately a third of patients were treated in non-ICU facilities, suggesting that these patients were less critically ill. Also, deaths were examined in a fairly short window between the initiation of iv. insulin and 24 h following the transfer to sc. dosing. Rates of major and minor hypoglycemia were 0.6 and 2.8%, respectively. The convenience of switching from iv. to sc. IAsp, rapid achievement of target BG and its safety profile were the main reasons physicians gave for preferring IAsp over the baseline treatment.

In some healthcare systems, rapid-acting insulin analogs may be more expensive than short-acting human insulins that may also be used for iv. administration, so this may need to be considered. However, it should be remembered that iv. treatment tends to be quite short; the mean duration of iv. treatment was 26 h and the mean dose was 80 units in this study. This study did not compare iv. IAsp with iv. short-acting human insulin and, as far as the authors are aware, no such studies exist; therefore, it is impossible to say whether IAsp demonstrates benefits compared to short-acting human insulins when administered iv.

Table 3. Physician preference to use intravenous insulin aspart therapy in the future.

Patient group	Physician preference to use iv. IAsp in the future	
	Prefer to use, n (%)	Prefer not to use, n (%)
Overall	2889 (99)	42 (1)
ICU	1926 (99)	19 (1)
Non-ICU	941 (98)	22 (2)
Known diabetic	2458 (98)	39 (2)
Nondiabetic	388 (99)	3 (1)
Type 1 diabetic	66 (100)	0 (0)
Type 2 diabetic	2280 (98)	39 (2)
Currently on insulin	1007 (99)	10 (1)
Currently not on insulin	1737 (98)	30 (2)
Currently on OAD	1615 (99)	17 (1)
Currently not on OAD	1079 (98)	23 (2)
Currently on neither insulin nor OADs	522 (97)	15 (3)
Most recent A1C <7%	132 (97)	4 (3)
Most recent A1C >7%	1695 (98)	33 (2)
Most recent blood glucose <11.1 mmol/l	409 (99)	5 (1)
Most recent blood glucose >11.1 mmol/l	2440 (99)	37 (1)
Experienced hypoglycemia with iv. IAsp	175 (99)	1 (1)
No hypoglycemia with iv. IAsp	2714 (99)	41 (1)
Experienced major hypoglycemia with iv. IAsp	48 (100)	0 (0)
No major hypoglycemia with iv. IAsp	2841 (99)	42 (1)
Experienced minor hypoglycemia with iv. IAsp	127 (99)	1 (1)
No minor hypoglycemia with iv. IAsp	2762 (99)	41 (1)

A1C: Glycated hemoglobin; IAsp: Insulin aspart; ICU: Intensive care unit; iv.: Intravenous; OAD: Oral antidiabetic drug.

Important benefits of using insulin analogs manifest themselves once patients are transferred to sc. insulins. The most important clinical advantage is the rapid lowering of BG by insulin analogs due to its pharmacokinetic action of fast absorption and dispersion from the sc. site of injection. Another important benefit of IAsp is the ability to inject it immediately before or after eating rather than 30 min before eating, as with soluble human insulin [14,15]. This convenience aspect could particularly benefit critically ill patients who may not have a predictable meal pattern. sc. IAsp administered every 1–2 h has been shown to be comparable with iv. regular insulin in the treatment of uncomplicated DKA [16]. This contrasts with a separate study in which sc. regular insulin was associated with delays in the reduction of plasma glucose compared with iv. regular insulin in the treatment of DKA [17]. A second study by Umpierrez *et al.* demonstrated improved glycemic control associated with the use of insulin analogs in a basal–bolus dosing regimen compared with the use of a sliding-scale insulin protocol with regular insulin [18]. However, these benefits may reflect the advantages of basal–bolus dosing regimens versus sliding-scale insulin as well as any benefits of insulin analogs versus regular insulin. Despite the fact that glycemic control was better with the insulin analog regimen, there were no differences in the rates of hypoglycemia in the two groups (3% in both) [18].

Conclusion

This study suggested that iv. IAsp was an effective and well-tolerated treatment for inpatient hyperglycemia. This was a large study of 3024 patients, which provides confidence in the findings; however, observational studies have inherent limitations and confounding factors, such as a lack of tightly controlled patient populations, no control groups and susceptibility to bias, that should also be considered. For example, there may be a confounding effect owing to the fact that physician-reported BG and glycated hemoglobin measurements were performed at each study site rather than by a central laboratory. A further limitation to this study, due to

Table 4. Physician reasons for preferring intravenous insulin aspart.

Patient group	Reason			
	Rapid achievement of target BG	Positive safety profile	Easy transfer from iv. to sc.	Other
Overall	2649	2334	2049	63
ICU	1754	1511	1302	32
Non-ICU	874	809	733	31
Known diabetic	2258	1984	1752	49
Nondiabetic	351	314	269	14
Type 1 diabetic	56	44	41	1
Type 2 diabetic	2105	1865	1640	48
Currently on insulin (n = 1040)	916	824	711	26
Currently not on insulin (n = 1797)	1590	1404	1230	37
Currently on OAD (n = 1662)	1474	1306	1156	37
Currently not on OAD (n = 1126)	991	882	750	25
Currently on neither insulin nor OADs (n = 550)	476	411	360	12
Most recent A1C <7% (n = 138)	99	97	73	0
Most recent A1C >7% (n = 1753)	1562	1466	1262	53
Most recent BG <11.1 mmol/l (n = 421)	378	273	251	3
Most recent BG >11.1 mmol/l (n = 2547)	2239	2032	1765	60
Experienced hypoglycemia with iv. IAsp	134	134	117	1
No hypoglycemia with iv. IAsp	2515	2200	1932	62
Experienced major hypoglycemia with iv. IAsp	27	40	21	1
No major hypoglycemia with iv. IAsp	2622	2294	2028	62
Experienced minor hypoglycemia with iv. IAsp	107	94	96	0
No minor hypoglycemia with iv. IAsp	2542	2240	1953	63

A1C: Glycated hemoglobin; BG: Blood glucose; IAsp: Insulin aspart; ICU: Intensive care unit; iv.: Intravenous; OAD: Oral antidiabetic drug; sc.: Subcutaneous.

its observational design, is the lack of a control group treated with a short-acting human insulin, for comparison of efficacy and safety. As this was an observational study, predefined BG targets differed between some of the study centers. Another limitation of this study, which reflects its observational design, is the lack of a defined iv. insulin protocol. Validated protocols with demonstrated efficacy and safety are available [2]. In this study, however, physicians were free to choose the iv. insulin protocol, which might have affected the outcomes in some patients. Observational trials have a number of advantages and limitations when it comes to analyzing SAEs. On the positive side, the high patient numbers and heterogeneous patient population mean that SAEs might be identified that would not be observed in smaller, more tightly controlled, randomized trials. In terms of limitations, the lack of randomization or a control group or means that it is more difficult to control for bias and confounding variables. Nevertheless, the SAEs observed in this study were fairly typical for a critically ill patient population and unlikely to be treatment related. Despite the limitations related to the observational design of the study, the study outcome is of interest as information on the use of iv. IAsp in the hospital setting is sparse. The results of this study support the development of future prospective, comparative, randomized, controlled trials examining the safety and efficacy of iv. IAsp in ICU and non-ICU settings.

Despite the limitations inherent in the observational trial approach, these data support iv. IAsp as an effective and well-tolerated option with a positive safety profile for managing inpatient hyperglycemia in ICU as well as non-ICU settings.

Financial & competing interests disclosure

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