Intensive Insulin Therapy in Postoperative Intensive Care Unit Patients

A Decision Analysis

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Rationale: Intensive insulin therapy (IIT) may reduce mortality in mechanically ventilated postoperative patients.

Objectives: To assess the risks and benefits of IIT in different institutions.

Design: Retrospective, blinded-to-outcome selection of patient cohorts from four hospitals.

Methods: Selection of a cohort of patients with clinical features similar to those reported in a recent study of IIT and of all mechanically ventilated postoperative patients from each hospital. Retrieval of information on glucose control. Assessment of risks and benefits and final outcomes.

Measurements and Main Results: We selected 783 consecutive patients with similar clinical and demographic features to the IIT trial control group and four general cohorts for a total of 4,150 consecutive mechanically ventilated postoperative patients. In these patients, glucose levels were measured 212,663 times for a mean value of 8.22 ± 2.7 mmol/L (148 ± 49 mg/dl). Intensive care unit (ICU) mortality varied from 2.2 to 13.6%. The incidence of hypoglycemia (defined as < 2.2 mmol/L) varied from 1.4 to 2.7%. Assuming a beneficial effect of IIT as reported, the number needed to treat to save one life varied from 38 in one ICU to 125 in another, whereas the rate of hypoglycemia (number needed to harm) varied from 7 to 13.

Conclusions: The number needed to treat to prevent an ICU death and the associated risk of hypoglycemia (number needed to harm) with IIT vary widely according to baseline mortality, case mix, and case selection. Rational decision analysis in individual ICUs should take these factors into account.

Keywords: critical care; critical illness; glucose; insulin; mortality, number needed to treat

Acute hyperglycemia is common in critically ill patients (1, 2). Control of glucose levels is considered important (3–6), and evidence exists on the possible benefits of better glucose control for patients with variable conditions (7–17). A recent study showed that ventilated postoperative intensive care unit (ICU) patients allocated to intensive insulin therapy (IIT) (target glucose: 4.4–6.1 mmol/L) had a 43% risk reduction in ICU mortality when compared with patients receiving conventional glucose control (mean glucose level: 8.49 mmol/L) (18). This study has led to the widespread adoption of protocols aimed at achieving and maintaining normoglycemia in ICU patients (19–25). However, some features of the IIT study (e.g., single-center, unblinded treatment; the administration of 200–300 g of intravenous glucose in the first 24 h; the routine early use of total parenteral nutrition; the potential harmful effects of hypoglycemia; the narrow population mostly made up of cardiac surgery patients; the high mortality in conventionally treated cardiac surgery patients; and the overall high mortality despite a relatively low mean Acute Physiology and Chronic Health Evaluation [APACHE] II score) invite caution in assuming the wider applicability of its findings. Furthermore, the risk/benefit ratio for IIT may change according to baseline mortality, patient selection, or the case mix of a given ICU (e.g., postcardiac surgery unit, neurologic ICU, post-transplant unit, trauma ICU, general ICU) (19, 26–30). Nonetheless, we considered applying IIT to our patients. To perform decision analysis, however, we selected a patient cohort to match the patients described in the IIT study and four other cohorts of consecutive mechanically ventilated postoperative patients from each participating hospital. In these five cohorts, with different case mixes and mortality, we assumed a benefit and risk equal to that reported in the IIT study and calculated the number needed to treat (NNT) and the number needed to harm (NNH). This article reports our findings.

METHODS

The data collection for this study is part of a long-standing quality assurance activity, for which the Austin Hospital Institutional Ethics Committee waives the need for informed consent.

Selection of Matched Cohort for IIT

Inception database. The current study was conducted as multicenter retrospective observational study. Hospitals A, B, and D are tertiary public hospitals in Melbourne and Sydney. Hospital C is a large private hospital in Melbourne. Cardiac surgery was performed in hospitals A, B, and D.

All patients admitted to these ICUs between February 2000 and October 2004 were included. The data used for the study were collected and electronically stored by specially trained and paid personnel as part of a high-quality national database system (Australian and New Zealand Intensive Care Society Adult Patient Database). After collection and entry, the data were corrected for logical errors and checked further by the central repository before acceptance. An Australian and New Zealand Intensive Care Society Adult Patient Database–modified APACHE III coding system was used for admission diagnosis. Audit of mortality and unit-based outcomes is ongoing for all four institutions.

We selected a patient cohort as similar as possible to that described in the IIT article (18) (postsurgical patients requiring mechanical ventilation with similar age, sex, diagnostic group, and APACHE II score) from our databases of 10,125 consecutive patients. All readmissions were removed before analysis. Selection was performed with blinding to outcome and according to predetermined rules. The details of this process are described in Appendix E1 and Table E1 of the online supplement.

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After all information was obtained, the patient list was matched to clinical outcomes.

**Assessment of NNT and NNH of IIT in different ICUs.** In the selected cohort and in each hospital, consecutive postoperative patients who received mechanical ventilation were then separated into eight diagnostic groups (a postcardiac surgery group and seven containing noncardiac surgery diagnostic groups). In each diagnostic group, mortality was assessed. To assess the risk/benefit of IIT in the selected matched cohort and in the different ICU cohorts, we developed a standardized approach based on diagnostic groups, specific mortality benefit of IIT, increased risk of hypoglycemia with IIT, and absolute mortality (see Table E2 in the online supplement).

**Glucose Values**
We obtained data on ICU glucose control. For all patients, all ICU glucose values (total of 212,663) during the entire ICU admissions were available. The blood glucose data used for this study was stored electronically and retrieved using the Bayer Rapidlink (Bayer Australia, Sydney, NSW, Australia) blood gas information management system.

**Approach to Insulin and Glucose Control**
There was no specific protocol for the use of insulin or any specific target for glucose control during the study period. The general goal was of maintaining glucose levels lower than 10 mmol/L. On admission, patients did not receive parenteral glucose infusion. If enteral nutrition support was possible, it was typically started within 48 h of admission.

**Data Description and Analysis**
Data are presented as mean ± SD or median with interquartile ranges, unless otherwise indicated. Differences between two groups were assessed using the χ² test. A p value less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using a commercially available statistical program, Statview (Abacus, Inc., Berkeley, CA).

**RESULTS**

**Assessment of Selected Matched Cohort**
We selected 783 postoperative patients that simulated all the clinical, demographic, and illness severity features reported in the IIT study. Table 1 shows the baseline characteristics of these patients. Although overall matching was excellent, the APACHE II score could not be fully matched and was higher in our cohort.

The entirety of ICU glucose measurements (n = 212,663) for all patients before selection (n = 10,125 patients) was available and the mean glucose concentration was 8.22 ± 2.70 mmol/L (148 ± 49 mg/dl). In the selection cohort (n = 783), glucose levels were measured 15,986 times for a mean value of 8.11 ± 2.40 mmol/L (146 ± 43 mg/dl), making mean blood glucose similar to the level reported for the “conventional treatment” group in the IIT study (Table 2). Such glucose control was consistent for each day of ICU stay (Figure 1). On average, blood glucose was measured approximately every 4 h (5.7 measurements/d). Hypoglycemia, defined as a blood glucose level of 2.2 mmol/L or less (40 mg/dl), occurred in 11 patients (1.4%). In keeping with expectations, 97.4% (763 patients) of selected patients had hyperglycemia (glucose > 6.1 mmol/L) on Day 1 and would have been eligible for treatment with the IIT protocol.

**Outcomes**
The mortality comparisons are displayed in Table 3. This table shows a low ICU mortality and hospital mortality among these matched patients. It also shows a low ICU mortality among patients from this cohort who required intensive care for more than 5 d. This low mortality was present for both cardiac surgery and noncardiac surgery patients. Intensive care for more than 14 d was also uncommon in our cohort. The rate of patients who required more than 14 d of mechanical ventilation was low, as was the incidence of sepsis (Table 4).

**Assessment of Mechanically Ventilated Postoperative Patients from Four ICUs**
Table 5 compared the NNT and NNH for IIT in 4,150 consecutive mechanically ventilated postoperative patients from the four participating ICUs, in the selected matched cohort of 783 patients, and in conventional glucose control group from the IIT study.

### TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Selected Matched Patients from our ICUs (n = 783)</th>
<th>Conventional Group (Intensive Insulin Trial) (n = 783)</th>
<th>Intensive Group (Intensive Insulin Trial) (n = 765)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>554 (71)</td>
<td>557 (71)</td>
<td>544 (71)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>62.5 ± 15.7</td>
<td>62.2 ± 13.9</td>
<td>63.4 ± 13.6</td>
</tr>
<tr>
<td>APACHE II score, median (IQR)</td>
<td>11 (9, 14)</td>
<td>9 (7, 13)</td>
<td>9 (7, 13)</td>
</tr>
<tr>
<td>Reason for ICU admissions, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>493 (63)</td>
<td>493 (63)</td>
<td>477 (62)</td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>59% of cardiac surgery</td>
<td>59% of cardiac surgery</td>
<td>59% of cardiac surgery</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>27% of cardiac surgery</td>
<td>27% of cardiac surgery</td>
<td>27% of cardiac surgery</td>
</tr>
<tr>
<td>Combined surgery</td>
<td>14% of cardiac surgery</td>
<td>14% of cardiac surgery</td>
<td>14% of cardiac surgery</td>
</tr>
<tr>
<td>Noncardiac indication</td>
<td>290 (37)</td>
<td>290 (37)</td>
<td>288 (38)</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>30 (4)</td>
<td>30 (4)</td>
<td>33 (4)</td>
</tr>
<tr>
<td>Trauma, or brain surgery</td>
<td>30 (4)</td>
<td>30 (4)</td>
<td>33 (4)</td>
</tr>
<tr>
<td>Thoracic surgery, respiratory insufficiency, or both</td>
<td>56 (7)</td>
<td>56 (7)</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Abdominal surgery or peritonitis</td>
<td>58 (7)</td>
<td>58 (7)</td>
<td>45 (6)</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>32 (4)</td>
<td>32 (4)</td>
<td>30 (4)</td>
</tr>
<tr>
<td>Multiple trauma or severe burns</td>
<td>35 (4)</td>
<td>35 (4)</td>
<td>33 (4)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>44 (6)</td>
<td>44 (6)</td>
<td>46 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (4)</td>
<td>35 (4)</td>
<td>35 (5)</td>
</tr>
<tr>
<td>Blood glucose on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6.1 mmol/L, n (%)</td>
<td>634 (81)</td>
<td>598 (76)</td>
<td>557 (73)</td>
</tr>
<tr>
<td>&gt; 11.1 mmol/L, n (%)</td>
<td>109 (14)</td>
<td>101 (13)</td>
<td>81 (11)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: APACHE II score = Acute Physiology and Chronic Health Evaluation (higher scores reflect more severe critical illness); ICU = intensive care unit; IQR = interquartile range.

To convert the values for glucose to milligrams per deciliter, divide by 0.05551.*
In the selected cohort, we found an ICU mortality of 1.1%. If one assumed the ICU mortality reduction reported with IIT, the NNT would be 102 to prevent an ICU death. In this cohort, if one assumed a 6.65 times increase in hypoglycemia with intensive glucose control as reported with the IIT protocol, there would be a 7.9% absolute increase in the incidence of this complication, with the number of patients needed to be treated to cause individual harm (NNH) being 13.

Blood glucose control was 8.29, 8.55, 7.88, 7.82, and 8.49 mmol/L in patients from hospitals A, B, C, and D, and the control group in the IIT study. These observations suggest a group of postoperative ICU patients with the aim of reproducing all the clinical features of the control group of a recent IIT study. These patients had a level of glucose very similar to the “control” group in the IIT trial. Hyperglycemia was ubiquitous. We found that, in this cohort, mortality and morbidity were lower than expected and the NNT was high. We then applied our analysis of NNT and NNH to four cohorts of consecutive mechanically ventilated postoperative patients from our hospitals. We found that the NNT and NNH varied widely, making IIT an unattractive strategy in one hospital and a viable one in another. These observations have important implications in terms of cost/benefit and risk/benefit ratios for the implementation of the IIT protocol in variable clinical environments elsewhere and require detailed discussion.

Our study has several strengths and limitations. First, this study was multicenter in nature. Second, glucose control was similar to that reported for the control cohort in the IIT trial. Hyperglycemia was ubiquitous. Nonetheless, despite our efforts, the study of four different hospitals, the use of a database of 10,125 admissions and the identification of five possible treatment cohorts for a total of 4,150 mechanically ventilated postoperative patients, our findings might be unique to Australia and the case mix of Australian ICUs. However, the aim of the current study is precisely to show the impact of such mortality and case mix variability on the NNT and NNH associated with the implementation of IIT.

Fewer of our patients might have had diabetes than in the IIT trial, thus improving outcomes. Unfortunately, the information in our database did not allow us to control for a history of diabetes. However, the rate of hyperglycemia at the time of admission to our ICUs was similar between our selected patients and the control group in the IIT study. This occurred despite

<table>
<thead>
<tr>
<th>TABLE 2. CONTROL OF BLOOD GLUCOSE LEVELS IN EACH GROUP</th>
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<tbody>
<tr>
<td><strong>Average of All Blood Glucose</strong></td>
</tr>
<tr>
<td>(Database Cohort)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
</tr>
<tr>
<td>No. measurements</td>
</tr>
<tr>
<td>No. measurements (d/person)</td>
</tr>
</tbody>
</table>

* Hypoglycemia was defined as a blood glucose level of 2.2 mmol/L or less.

To convert the values for glucose to milligrams per deciliter, divide by 0.05551.

§ Selection cohort was the patient group (783 patients) selected from the database after matching to the conventional treatment group in the IIT study.

**Definition of abbreviations:** CI = confidence interval; ICU = intensive care unit; IIT = intensive insulin treatment study; N/A = not available.

We also studied four cohorts from four different hospitals with a varied case mix. We included all mechanically ventilated postoperative patients as in the IIT study. We found a similar level of glucose control, but much variability in the calculated NNT. Nonetheless, despite our efforts, the study of four different hospitals, the use of a database of 10,125 admissions and the identification of five possible treatment cohorts for a total of 4,150 mechanically ventilated postoperative patients, our findings might be unique to Australia and the case mix of Australian ICUs. However, the aim of the current study is precisely to show the impact of such mortality and case mix variability on the NNT and NNH associated with the implementation of IIT.

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**DISCUSSION**

We conducted a decision analysis for the application of IIT. The aim was to assess the wider applicability and risk/benefit implications of treating patients in our institutions. We selected...
the fact that intravenous glucose was not routinely administered on Day 1 to our patients, as was the case in the IIT study. Fewer of our patients might have had cancer or been referrals for tertiary care. Unfortunately, we could not identify a history of cancer or the rate of tertiary referral in our cohort. However, our hospitals are tertiary referral centers and we have no reason to believe that the incidence of cancer would be less in our population.

Our patients might have been less ill than those in the IIT trial and this difference might explain the lower mortality in our selected group. However, diagnostic groups were identical and represent a marker of the overall adequacy of care. Whether the same benefit would be seen in patients receiving more conventional nutrition is unknown. However, our study focused on how the NNT of IIT would vary according to case mix and mortality rate and assumed that IIT would have the same benefit during conventional nutrition.

Our selected cohort had a lower incidence of sepsis compared with the intensive treatment group in the IIT trial. This might be one of the reasons our mortality rate was lower. IIT might be particularly beneficial in septic patients (18, 34). On the other hand, sepsis might increase during total parenteral nutrition (35, 36) and represent a marker of the overall adequacy of care. Also, in our selection, medical patients (higher mortality and APACHE II score) were excluded. However, little information is available on the effect of IIT in such patients. Whether the same treatment effect would be seen in patients with the intensive treatment group in the IIT trial. This might be one of the reasons our mortality rate was lower. IIT might be beneficial in septic patients (18, 34). On the other hand, sepsis might increase during total parenteral nutrition (35, 36) and represent a marker of the overall adequacy of care. Also, in our selection, medical patients (higher mortality and APACHE II score) were excluded. However, little information is available on the effect of IIT in such patients. Whether the same treatment effect would be seen in patients with sepsis or other conditions similar to those in the IIT trial.

In the IIT trial, all patients received early and continuous intravenous glucose (200–300 g/d), often followed by combined total parenteral and enteral nutrition. Neither the use of high-dose intravenous glucose nor the early institution of parenteral nutrition is common in Australia (31) or other countries (32) or supported by evidence (33). The management of nutrition in the IIT trial may have led to an iatrogenic increase in the incidence of hyperglycemia, resulting in greater insulin administration. The management of nutrition in the IIT trial may have led to an iatrogenic increase in the incidence of hyperglycemia, resulting in greater insulin administration. Whether the same treatment effect would be seen in patients receiving more conventional nutrition is unknown. However, our study focused on how the NNT of IIT would vary according to case mix and mortality rate and assumed that IIT would have the same benefit during conventional nutrition.
for matching, had to span between February 2, 2000, and July 9, 2004. None of the patients in our cohort, however, received recombinant human activated protein C or steroid therapy for sepsis. No other therapies have been shown to improve the outcome of postoperative ICU patients since 2000.

Because the selected matched cohort of 783 only represented a restricted approach to decision analysis (policy of very specific and targeted selection of patients for IIT), we then expanded our analysis to a broader group of patients from our four hospitals who might be candidates for IIT if the treatment was broadly applied to all patients who were mechanically ventilated and postoperative.

We found that, according to unit case mix and mortality, the NNT and NNH varied greatly. In hospitals A and C, most patients were postcardiac surgery patients. In both, mortality was low (1.2 and 0.5%) in comparison with 5.1% in the IIT control group. Therefore, the NNT was significantly higher at 104 and 0.5% in comparison with 5.1% in the IIT control group. This highlights another aspect of the risk/benefit relation-

TABLE 4. MORBIDITY OF STUDY PATIENTS

<table>
<thead>
<tr>
<th>Duration of intensive care, d</th>
<th>Selected Matched Patients From Our ICUs (n = 783)</th>
<th>Conventional Treatment (Intensive Insulin Trial) (n = 783)</th>
<th>Intensive Treatment (Intensive Insulin Trial) (n = 765)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2 (2, 5)</td>
<td>3 (2, 9)</td>
<td>3 (2, 6)</td>
</tr>
<tr>
<td>Patients receiving intensive care for ≤ 5 d</td>
<td>2 (1, 3)</td>
<td>2 (2, 3)</td>
<td>2 (2, 3)</td>
</tr>
<tr>
<td>Patients receiving intensive care for &gt; 5 d</td>
<td>8 (7, 13)</td>
<td>15 (9, 27)</td>
<td>12 (8, 20)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (d)</td>
<td>39/783 (4.9%)</td>
<td>123/783 (15.7%)</td>
<td>87/765 (11.4%)</td>
</tr>
<tr>
<td>Sepsis during ICU stay</td>
<td>10/783</td>
<td>61/783</td>
<td>32/765</td>
</tr>
</tbody>
</table>

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range; N/A, not available for 95% confidence intervals. Morbidity was described as days, median (IQR), or n/total n (%), with 95% confidence interval in parentheses.

TABLE 5. CALCULATION OF NUMBER NEEDED TO TREAT AND THE NUMBER NEEDED TO HARM OF INTENSIVE INSULIN TRIAL IN SIX DIFFERENT CASE-MIX GROUPS

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Mean blood glucose, mmol/L</th>
<th>ICU mortality, %</th>
<th>Incidence of hypoglycemia, %</th>
<th>NNT (95% CI)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.29 ± 2.85</td>
<td>5.6</td>
<td>2.7</td>
<td>104 (73-178)</td>
<td>56.5 (6-7)</td>
</tr>
<tr>
<td>B</td>
<td>8.55 ± 2.88</td>
<td>13.6</td>
<td>2.2</td>
<td>38 (22-139)</td>
<td>0 (6-12)</td>
</tr>
<tr>
<td>C</td>
<td>7.88 ± 2.46</td>
<td>2.2</td>
<td>1.8</td>
<td>125 (51-N/A)</td>
<td>82.6 (8-12)</td>
</tr>
<tr>
<td>D</td>
<td>7.82 ± 2.46</td>
<td>11.5</td>
<td>1.4</td>
<td>38 (26-68)</td>
<td>2.1 (10-17)</td>
</tr>
<tr>
<td>E</td>
<td>8.11 ± 2.42</td>
<td>2.2</td>
<td>1.4</td>
<td>102 (60-345)</td>
<td>63.0 (10-17)</td>
</tr>
<tr>
<td>F</td>
<td>8.49 ± 1.83</td>
<td>8.0</td>
<td>0.77</td>
<td>29 (21-46)</td>
<td>63.0 (17-34)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; IIT = intensive insulin therapy; N/A = not available; NNH = number needed to harm; NNT = number needed to treat.

The incidence of hypoglycemia (per patient) was defined as less than 2.2 mmol/L.
Our study does not in any way signify that IIT is an ineffective intervention to improve mortality or morbidity in postoperative ICU patients. It simply invites caution in applying its findings to similar patients from other hospitals or countries where, for reasons of patient mix and comorbidity distribution, mortality might be lower, the NNT much higher, and NNH lower (22). Conversely, if one assumes that IIT has the same benefit on patients treated with conventional nutritional support, it suggests that, in some settings, with the right case mix, the introduction of IIT might be a desirable option. The cutoff point of NNT and NNH at which the introduction of IIT is appropriate obviously requires additional considerations such as cost, availability of point of care testing, availability of nursing staff, and workload assessment.

A large prospective multicenter collaborative study investigating intensive glycemic control in the critically ill is well under way. The study called NICE (Normoglycemia in Intensive Care Evaluation) is scheduled to randomize 4,000 patients in 20 ICUs in Australia and New Zealand (see http://www.controlled-trials.com/isrctn/trial//0/04968275.html).

NICE is now likely to be joined by a Canadian group of ICUs soon to become NICE-SUGAR (Surviving Using Glucose Algorithm Regulation) and should randomize perhaps another 500 to 1,000 patients. This study will provide information on the effect of normoglycemia in a heterogeneous (medical and surgical) group of critically ill patients treated with conventional nutritional support. This larger multicenter study should provide more definitive information on the NNT and NNH in different clinical settings.

In conclusion, we found that, in a cohort of patients that mimicked the IIT study patients, the NNT would have been high at 102 to prevent one ICU death at the cost of approximately nine cases of hypoglycemia. However, when broader criteria were applied to selection and cohorts of mechanically ventilated postoperative patients were studied from four different hospitals, we found that the NNT varied from 38 to 125. In our opinion, these observations suggest that different institutions should carefully consider formal decision analysis of the possible benefits and risks of IIT in their surgical patients before implementing an IIT protocol.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References


