Intensive Insulin Therapy in Severe Acute Pancreatitis: A Meta-analysis and Systematic Review

J Li, TR Chen, HL Gong, MH Wan, GY Chen, WF Tang

ABSTRACT

Objective: *To assess the effect of intensive insulin therapy on outcomes of patients with severe acute pancreatitis.*

Methods: *Relevant literatures cited in these electronic databases: Medline, Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI) database, and Excerpta Medical database (Embase) were systematically searched for randomized controlled trials (RCTs) in which intensive insulin therapy was used in severe acute pancreatitis. Length of hospitalization, acute physiology and chronic health evaluation II (APACHE II) score, incidence of complications, and adverse effects were recorded for statistical analysis. The methodological quality of the eligible studies was assessed by Jadad scale. The results were analysed by Revman 4.3 software.*

Results: *Three studies, which included a total of 118 cases, were finally reviewed. The methodological quality of the trials varied substantially. In patients with severe acute pancreatitis, intensive insulin therapy was associated with shorter length of hospitalization (weighted mean difference (WMD) = -12.13, 95% confidence interval (CI) [-15.48 , 8.78],* $p > 0.00001$ *) and lower APACHE II score after 72 hours treatment (WMD = -3.80, 95% CI [-4.88 , 2.72],* $p > 0.00001$*). One study reported insulin-related adverse event.*

Conclusion: *In patients with severe acute pancreatitis, intensive insulin therapy could relieve the patient's condition earlier and shorten the length of hospitalization without serious adverse effect.*

Keywords: Conventional insulin therapy, intensive insulin therapy, severe acute pancreatitis

Terapia Intensiva de Insulina en la Pancreatitis Aguda Severa: Meta-análisis y Revisión Sistemática

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RESUMEN

Objetivo: *Evaluar el efecto de la terapia intensiva de insulina en la evolución clínica de los pacientes afligidos de pancreatitis aguda severa.*

Métodos: *La literatura pertinente citada a partir de las siguientes bases electrónicas de datos: Medline, Base de datos de literatura biomédica china, Base de datos de la infraestructura nacional china de conocimientos (CNKI), y la Excerpta Medical Database (Embase). Todas estas bases de datos fueron investigadas sistemáticamente en busca ensayos controlados aleatorios (RCT), en los cuales la terapia de insulina intensiva se usó en la pancreatitis aguda severa. El tiempo de hospitalización, la fisiología aguda, y la puntuación de la evaluación de salud crónica II (APACHE II), la incidencia de complicaciones, así como los efectos adversos, fueron registrados para el análisis estadístico. La calidad metodológica de los estudios elegibles fue evaluada mediante la escala de Jadad. Los resultados se analizaron mediante el software Revman 4.3.*

Resultados: *Finalmente se examinaron tres estudios que incluyeron un total de 118 casos. La calidad metodológica de los ensayos varió sustancialmente. En los pacientes con pancreatitis aguda severa, la terapia de insulina intensiva estuvo asociada con una estadía hospitalaria más corta (diferencia*

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media ponderada WMD = -12.13, 95% intervalo de confianza (CI) [-15.48, 8.78], p < *0.00001) y una puntuación APACHE II más baja después de 72 horas de tratamiento (WMD = -3.80, 95% CI [-4.88, 2.72],* p < *0.00001). Un estudio reportó eventos adversos relacionados con la insulina.*
Conclusión: *En los pacientes con pancreatitis aguda severa, la terapia intensiva de insulina podría aliviar la condición del paciente más rápidamente, y acortar el tiempo de hospitalización sin serios efectos adversos.*

Palabras claves: Terapia convencional de insulina, terapia intensiva de insulina, pancreatitis aguda severa

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INTRODUCTION

Severe acute pancreatitis (SAP) is one of the most common critical diseases with a high rate of complications, morbidity and mortality. With deeper understanding of the essence of the disease and the improvement of intensive care technology, the current mortality rate of SAP has been reduced to 10% – 30% (1, 2). As a result of pancreatic damage in patients with stress and inflammatory response (3), hyperglycaemia is common in the early stage of acute pancreatitis (4). The level of blood glucose is a sensitive indicator of the severity of acute pancreatitis (5). Severe acute pancreatitis is often complicated by abnormal glucose tolerance, hyperglycaemia and even ketoacidosis, which could affect the development and prognosis of the disease. Thus, strict control of blood glucose should be vital for the patients with SAP (6, 7). Currently, the efficacy of conventional blood glucose control without intensive monitoring is not satisfactory in SAP (8) and increasing attention has been paid to intensive insulin therapy (IIT) in severe patients (9). Gradually, some randomized controlled clinical trials with IIT were carried out in SAP in China. However, the efficacy of IIT for SAP has not been adequately evaluated by validated randomized controlled trials (RCTs) abroad or systematic reviews. This study was designed to evaluate the effect of IIT in SAP through a systematic review with RCTs from 1989 to 2010. Its aim is to provide new evidence for the management of SAP with IIT.

SUBJECTS AND METHODS

A computerized literature search of the China National Knowledge Infrastructure (CNKI) database, Chinese Biomedical Literature Database, the network databases such as Medline and Excerpta Medical database (Embase) was conducted from January 1989 to December 2010. The keywords used to search Chinese database were "acute pancreatitis" and "intensive insulin therapy". The keywords for Medline and Embase were "acute pancreatitis" and "insulin", "acute pancreatitis" and "intensive insulin treatment", "severe acute pancreatitis" and "intensive insulin therapy". In addition, we retrieved a variety of journal papers and conference proceedings about SAP, and tracked the appendix references in research papers, and tried our best to get contact with relevant experts and staff for research literature.

To identify published studies for inclusion in this review, these were the following inclusion criteria: (i) study design: randomized controlled trials, (ii) population: patients with acute pancreatitis, (iii) interventions: conventional treatment as the control group (conventional treatment including fluid resuscitation, prophylactic use of antibiotics and nutritional support *etc*) with the target blood glucose level at 10.0–11.1 mmol/L (10) *versus* 4.4–6.1 mmol/L in the IIT treatment group, (iv) outcome measures – primary outcome measures: length of hospitalization, significant decreased time of acute physiology and chronic health evaluation II (APACHE II) score. Secondary outcome measures: incidence of complications and adverse effects. Patients were excluded if they had: (i) been undergoing a mild course of the disease in accordance with the consensus of Atlanta (11), (ii) primary epilepsy or mental illness, serious heart, liver, kidney, brain diseases affecting primary effect of evaluators and were pregnant or breastfeeding.

Two reviewers (the first two authors of this article) independently identified potentially eligible trials according to the inclusion criteria with the same quality evaluation scale and made cross-checks. If there was any disagreement, a third reviewer (MH Wan) would be consulted to come to a consensus. If there was something unknown in the material, the original author was to be contacted for relevant information. The methodological quality of included studies was assessed by Jadad score scale (quality score range from 0–5). The research team made strict quality evaluation on the initial inclusion of each RCT literature; those which could not be completely identified as randomized controlled trials were of no score.

Data were processed by Review Manager (RevMan 4.3; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration). Enumeration data were described by relative risk (RR) with corresponding 95% confidence interval (95% CI). Continuous variable data were described by weighted mean difference (WMD) or standardized mean difference (SMD), with corresponding 95% CI. I^2 measure was used to describe heterogeneity ($I^2 > 50\%$ indicating significant heterogeneity). A random effect model was applied despite the degree of heterogeneity. Analysis of each index to evaluate the efficacy followed the intention to treat (ITT) principle.

Assessment of publication bias and sensitivity analysis was not performed to examine the pooled results because of the limited number of trials.

RESULTS

An initial search identified 114 potentially relevant articles of which three studies met the inclusion criteria and were thus subjected to our systematic review. Sixty-four articles were excluded because their publication was duplicated. Another 41 articles did not meet the inclusion criteria. The remaining nine articles were further evaluated by considering whether they used the primary outcome measurements of hospitalization and APACHE II score after treatment. Those articles that did not use these two measurements were excluded. This left four articles for review; one was excluded because of the obvious difference of the study subjects (all of them were patients over 70 years old). A final of three studies remained for review, all of which were published RCTs in Chinese, with 118 participants (62 cases in IIT group, 56 in conventional insulin therapy group). All of the three studies were comparisons between an IIT group and the conventional treatment group. The literature retrieval process is summarized in Fig. 1. Features of the included studies are shown in Tables 1 and 2. The main outcomes of the studies are summarized in Table 3 and the methodological quality of included studies in Table 4.

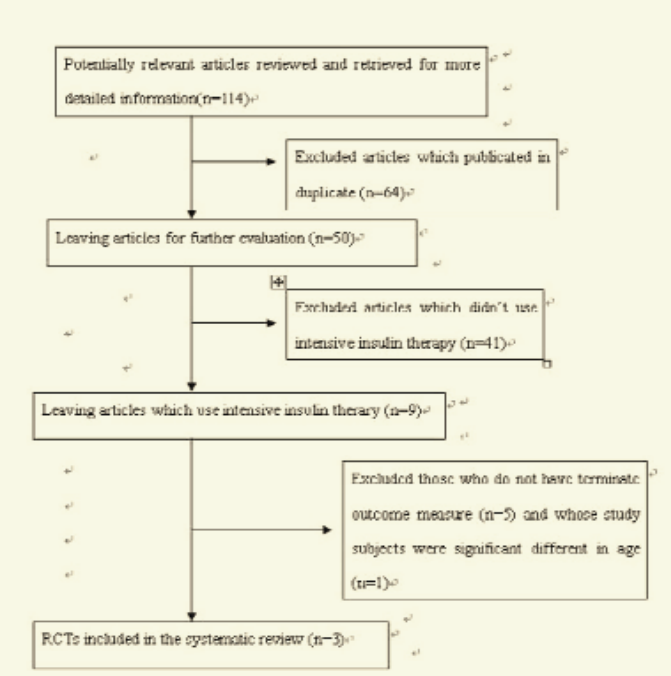

Fig. 1: Flow diagram showing studies included and excluded from the systematic review.

Table 1: Character of included studies

Researcher	Inclusion criteria (number)	Intervention		Outcome measurement
		IIT Group	CIT Group	
Tao and Li 2006 (11)	Chinese guidelines for the management of acute pancreatitis 21/21	WAN DENBERCHE Programme of Intensive Insulin Therapy (13)	Blood glucose target 10.0 ~ 11.1 mmol/L	Length of hospitalization, mechanical ventilation time, APACHE II score, infection rate and mortality
Liu *et al* 2010 (14)	Chinese guidelines for the management of acute pancreatitis 23/22	WAN DENBERCHE Programme of Intensive Insulin Therapy	Blood glucose target 10.0 ~ 11.1 mmol/L	Length of hospitalization, APACHE II score, mortality
Qiu and Wang 2008 (15)	Chinese guidelines for the management of acute pancreatitis 18/13	WAN DENBERCHE Programme of Intensive Insulin Therapy	Blood glucose target 10.0 ~ 11.1 mmol/L	Haemodiastase, urinary amylase, blood, blood biochemistry, APACHE II score, length of hospitalization, complications

IIT: intensive insulin therapy, CIT: conventional insulin therapy, APACHE II: acute physiology and chronic health evaluation II.

Table 2: Demographic characteristics

Study	Total patients	Gender Men	Women	Age (year)	Severity (mean score)
Tao and Li	42	22 (52%)	20 (48%)	18–76	13.22 (APACHE II)
Liu *et al*	45	24 (53%)	21 (47%)	26–81	12.46 (APACHE II)
Qiu and Wang	31	19 (61%)	12 (39%)	17–77	17 (APACHE II)

Table 3: Main outcomes of the studies

Study	Tao and Li		Liu *et al*		Qui and Wang	
Group	IIT group (n = 21)	CIT group (n = 21)	IIT group (n = 23)	CIT group (n = 22)	IIT group (n = 18)	CIT group (n = 13)
Outcomes						
APACHE II 1 day	12.95 ± 3.56	13.48 ± 3.18	12.7 ± 3.3	12.2 ± 3.1	13 ± 3	15 ± 3
APACHE II 3 day	10.02 ± 3.08	14.48 ± 3.56	10.2 ± 2.6	14.2 ± 3.3	10 ± 2	13 ± 3
LOH (day)	35.72 ± 8.56	51.64 ± 11.92	40.8 ± 8.9	53.5 ± 11.4	32 ± 9	41 ± 6
Death	6 (28.57%)	7 (33.33%)	6 (26.1%)	6 (27.3%)	1 (5.6%)	1 (7.7%)

IIT – intensive insulin therapy, CIT – conventional insulin therapy, LOH – length of hospitalization

Table 4: Quality assessment of the studies

Researcher	Randomization	Allocation Concealment	Blind	Baseline Similarity	Lost/Quit	Compliance	JADAD score
Tao and Li	Semi-randomization	Unclear	Unclear	Yes	Not mentioned	Not mentioned	0
Liu *et al*	Semi-randomization	Unclear	Unclear	Yes	Not mentioned	Not mentioned	0
Qui and Wang	Not described	Unclear	Unclear	Yes	Not mentioned	Not mentioned	1

Evaluation was carried out to compare the length of hospitalization, APACHE II score significantly decreased time, and adverse effects. With combined WMD -12.13 and 95% CI [-15.48-, -8.78], a shorter length of hospitalization was seen in the intensive insulin group [$p < 0.00001$] (Fig. 2). Likewise, APACHE II score, after 72 hours treatment, decreased faster in the intensive insulin group with corresponding WMD -3.80, 95% CI [-4.88, -2.72], which suggested a significant difference [$p < 0.00001$] (Fig. 4). However, on the first day of allocation, there was no significant difference ($p = 0.34$) in APACHE II score with combined WMD -0.57, 95% CI [-1.72, 0.59] which could further demonstrate that IIT has a better effect (Fig. 3). Overall, only one paper mentioned that hypoglycaemia occurred in the IIT group, and no serious consequence occurred after timely management.

The remaining studies did not describe the incidence of adverse effect, so combined analysis could not be performed with adverse effect.

DISCUSSION

In this review, we specifically focussed on RCTs that investigated the efficacy of IIT in SAP. Compared to conventional

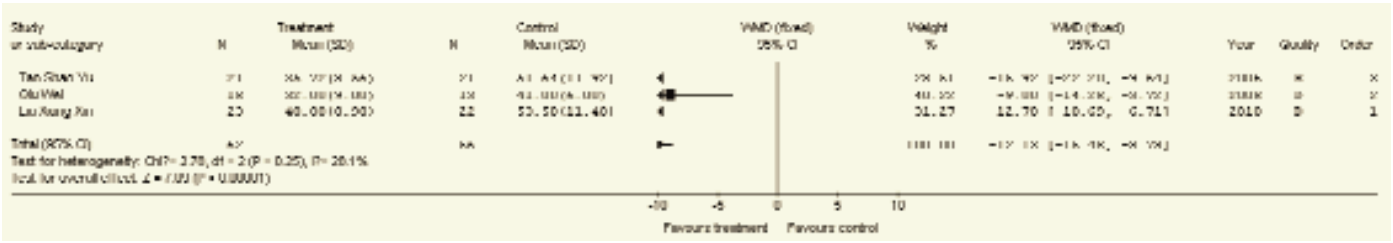

Fig. 2: Comparison of length of hospitalization between IIT group and CIT group.

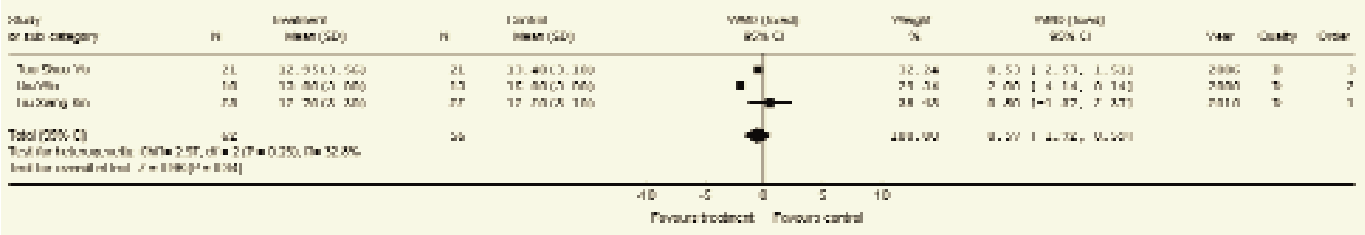

Fig. 3: Comparison of APACHE II score on the first day of allocation between IIT and CIT groups.

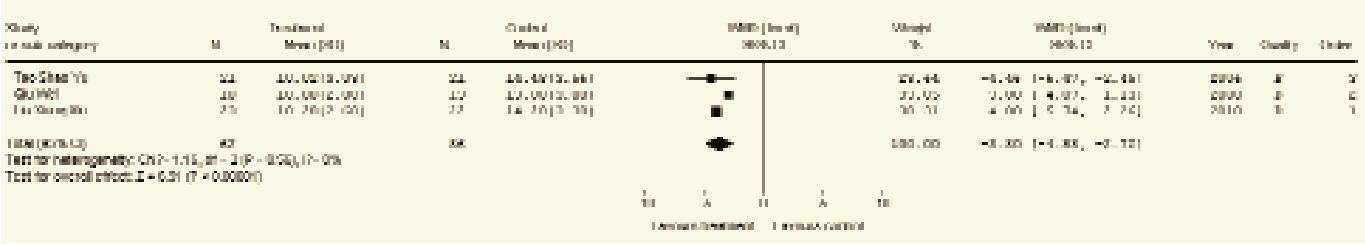

Fig. 4: Comparison of APACHE II score after 72 hours treatment between IIT and CIT group.

insulin therapy, IIT was superior for controlling blood glucose in patients with SAP. It could decrease the APACHE II score faster and shorten the length of hospitalization, and eventually improve the clinical outcome.

The likely mechanism of prognostic improvement by IIT might be interpreted as follows: (i) decrease in the release of inflammatory mediators, and lowering of the incidence of pancreatic infection, (ii) improve immunoparalysis in the presence of stress *via* upregulating the expression of human leukocyte antigen-DR (HLA-DR) on monocytes and decreasing cell apoptosis (16, 17), (iii) enabling the pancreas to have a rest by supplemental insulin, (iv) protecting against mucosal barrier dysfunction and reduce bacterial translocation.

Currently, the importance of blood glucose control to critically ill patients has been widely recognized. Though application of IIT is controversial, according to most researchers it is necessary to have tight blood glucose control of critically ill patients (18). Since the benefit of IIT was first demonstrated by a single-centre trial in Leuven, Belgium (13), a series of clinical control trials have been conducted since then to explore the effect of IIT. However, the results are conflicting. In spite of some positive results from a few later studies (19–21) and some Chinese studies, the effect of IIT was not accepted by recent researchers because of the high incidence of hypoglycaemia (8 to 28%) and inapparent effect on rates of secondary outcomes (renal impairment, duration of mechanical ventilation, infection rate, length of hospitalization *etc*) as well as increased mortality (22–26). The results of the present study do suggest that IIT may be more effective for patients with SAP. The results were limited, however, because of the following problems: firstly, the number of trials was small, although there was a thorough search in English databases, Chinese databases and unpublished postgraduate thesis databases. The studies had many methodological flaws, such as no description of study design, no mention of random allocation generation, allocation concealment and blinding, no description of basic disease, no report on patient withdrawal, no mention of ITT analysis, no estimation of sample size *etc*. Also, all three studies compared the conventional treatment group with the intensive treatment group, but no placebo control group. According to the literature, a proportion of 30% ~ 34.2% of non-diabetic patients with acute pancreatitis was hyperglycaemic (27). As there are many factors that affect the blood glucose level in the early stage of acute pancreatitis, a placebo control group might have contributed to better assessment of the efficacy of IIT in SAP. In addition, adverse events were not provided accurately. Among the included studies, only one referred to the occurrence of hypoglycaemia in the IIT group, but without determining the standard of hypoglycaemia – there was literature regarding blood glucose < 2.2 mmol/L as standard (24) – without mentioning whether blood sample was obtained for laboratory comfirmation at the time hypoglycaemia occurred, and without making comparison between the IIT group and the conventional insulin therapy group in the incidence of hypoglycaemia. Secondly, this review has its limitations. Commonly used indicators to evaluate the severity of SAP are: severity (APACHE II score, Ranson's score), mortality, complication incidence, surgery rate, length of hospitalization and hospital costs. In the studies included, Tao and Li (11) used length of hospitalization (LOH), mechanical ventilation time, APACHE II score, and pancreatic infection rate and mortality as outcome measures; Liu *et al* (14) used LOH, APACHE II score and mortality as outcome measures; Qiu and Wang (15) used amylase, blood biochemistry, APACHE II score, LOH and complication incidence as outcome measures. When determining the outcome measures, this study adopted LOH and APACHE II score significantly decreased time as the main observation indicator in order to assure the review's quality and to unify the standard of treatment efficacy because of the different outcome measurement that the three studies adopted. In addition, there were studies using the concentration of serum inflammatory mediators (1, 28) and immune function as clinical indicators to assess the efficacy of IIT in SAP (29). As they were not terminal indicators for clinic practice, these studies were excluded from this systematic review. This partly contributed to the limited number of trials.

In conclusion, this review has identified that IIT could shorten LOH and decrease APACHE II score faster compared to conventional therapy in patients with SAP. However, lack of placebo-control, small number of trials, limited sample size and poor quality of the literature made it difficult to generate reliable conclusions about the efficacy of IIT. So the accuracy of this review needs to be confirmed by more rigorously designed and larger sample size RCTs to further evaluate the effects of IIT in SAP.

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