



(REVIEW ARTICLE)



## Challenges of the intensive insulin therapy in experimental models of extensive burn injury

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Publication history: Received on 23 July 2020; revised on 03 August 2020; accepted on 06 August 2020

Article DOI: <https://doi.org/10.30574/wjarr.2020.7.2.0277>

### Abstract

Burn injuries (BI) above 40% of total body surface area (TBSA) are considered extensive and associated to systemic responses. The intensive insulin therapy (IIT) has been chosen as treatment because of its anabolic and anti-inflammatory properties, and by glycemic control. Several experimental models of extensive BI with IIT has just been studied, however they have many variables and challenges. Thus, this review aims to investigate the animal models of extensive BI with IIT, in order to better understanding benefits and limitations of this therapy. The review of papers published on the literature and indexed on the PubMed database was conducted by searching the keywords predetermined. Insulin administration after BI is able to revert hyperglycemia state, accelerate wound healing, decrease the mRNA expression of some pro-inflammatory cytokines, attenuate acute lung injuries, decrease inflammation in intestinal epithelium and attenuate the muscle loss. We can conclude, although there are limitations related to burn standard or insulin administration, the systemic benefits of IIT overcome limitations.

**Keywords:** Burn; Insulin; Metabolism; Intensive insulin therapy; Insulin resistance.

### 1. Introduction

Burns injuries (BI) are highly debilitating traumas, causing about 265,000 deaths per year in the world [1]. In Brazil occurred an average 25,000 hospitalizations for burns and corrosion between 2010 until 2015, which generated high government spending [2]. Extensive BI have great relevance especially in children, being scalding case the most common, principally in domestic environments [3].

Burns covering more than 30% total body surface area (TBSA) are associated to intense stress, inflammation and hypermetabolism, with consequent insulin resistance (IR) and hyperglycemia. These symptoms can affect the healing of the wound and causes development delay and other complications for about to 2 years. Furthermore, predisposes to complication various, as severe and fatal infections [4,5].

The main severe response of BI is the hypermetabolic state and protein losses, which resulted of increased protein degradation more than synthesis, and the second major response is hyperglycemia state [6]. Thus, several treatments have been used for glycemic control, such as insulin because of its anabolic and anti-inflammatory properties [7].

Despite its beneficial effects, the intensive insulin therapy (IIT) has been a point related to much controversy, because it leads to a risk of hypoglycemia [8] which can be more dangerous than hyperglycemia due to BI [8,9]. Therefore, this review aims to investigate the animal models of extensive BI with IIT, in order to better understand the benefits and limitations of this therapy.

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## 2. Methods

A computerized literature search was done in PubMed-Medline database. The keywords that we used were Burn, either Thermal Injury or Scald. Together another group of keywords related to IIT: Intensive Insulin Treatment or Therapy, Detemir, Glargine, Lantus, NPH, protamine, Iletin and Insulin. After that, we selected to read the complete paper in Portuguese, English and Spanish. Other languages were not considered. As an excluding criteria, the papers with euthanasia of animals for a minimum for 24 hours post injury, i.e. experimental models that received IIT at least 1 day or more. Thus, 14 papers were presented in Table 1, considering the percentage of TBSA scalding injury.

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## 3. Results

### 3.1. Systemic responses after extensive burn injury

BI over 40% of body extension are considered extensive and result in the local and systemic responses [10]. The extensive BI are followed by long periods of stress, inflammation and hypermetabolism, characterized by increase of the hypermetabolic state such as glycolysis, proteolysis, lipolysis, glycogenolysis, and gluconeogenesis [6,11]. In addition, there is a significant increase in the energetic expenditure, which is not supplied by catabolic state during hypermetabolism [12,13], resulting in an imbalance of the use and the availability of the energy [10]. The hypermetabolic state elevates energy expenditure to maximum at 10 days after BI [14], remaining altered for two years post-burn in children [5].

Besides, several authors mention that immune dysfunction [15], acute IR, hyperglycemia [16], protein catabolism, muscle atrophy [12,13,17], hepatocyte degeneration [18] and decreased bone mineral content [5] are characteristics of BI systemic response.

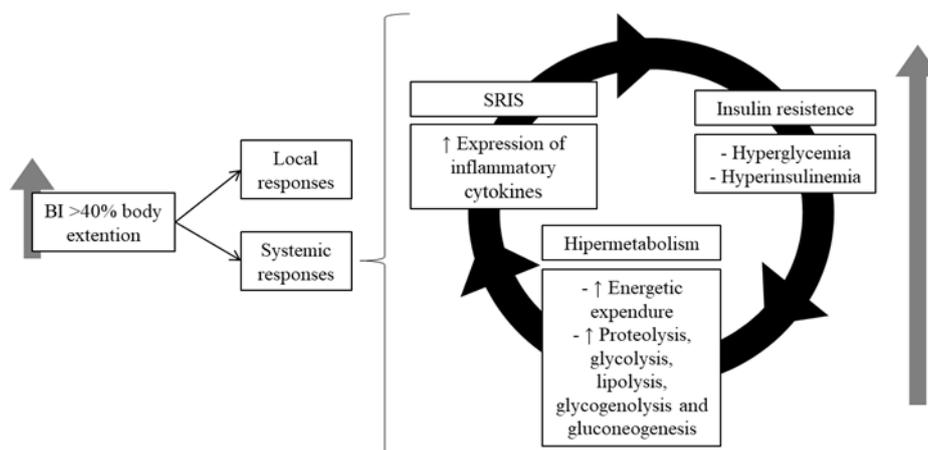
Severe BI also are associated to increased expression of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL1-6) and cyclooxygenase [5,14,19]. These inflammatory mediators induce systemic inflammatory response syndrome (SIRS) that leads to hypermetabolism, hemodynamic alterations, and increased energetic expenditure. These alterations can result in infection and sepsis with high risk of multiple-organ failure and death [10].

Oxidation energy substrates in mitochondrial respiration produce excessive formation of reactive oxygen species resulting oxidative stress, which together with the increased level of inflammatory mediators, promote IR [20] or pseudodiabetes [21].

After 3 or 4 days of the BI, the dependent tissues of the insulin, such as skeletal muscle and fat, develop an IR [22] that persist for several weeks [21,23]. In addition, the cellular stresses caused by extensive BI also active neuroendocrine response that increase the release of hormones as catecholamine, glucagon and cortisol [6].

In normal condition, insulin signaling on skeletal muscles and fat occurs via insulin receptor/insulin receptor substrates/phosphatidylinositol 3-kinase/protein kinase B (IR/IRS/PI3K/Akt) and translocation of glucose transporter - 4 (GLUT-4) to membrane, allowing the entry of glucose for facilitated diffusion [24]. After extensive BI, there are changes in the receptor insulin signaling, more specifically in phosphorylation of IRS-1 resulting to decrease glucose uptake [21,25].

The absence of glucose uptake adequate in the cell lead to increased plasmatic glucose and, consequently elevated rate of body glucose production. Thus, a hyperglycemia is a risk factor to burn patients, because it helps to keep the hypermetabolism [6]. These alterations leads to predisposition to complications, such as development of infections that complicate the rehabilitation and increase the mortality [16,26]. The Figure 1 schematizes the extensive BI responses, which involves from local consequences until systemic, creating cycle where the more injury extension, more extended responses.



**Figure 1** Extensive burn injury and systemic alterations cycle.

### 3.2. Intensive insulin therapy after extensive burn injury

For patients with extensive BI, glycemic control can be maintained by IIT [4,27-29]. This therapy has been used to control IR and hyperglycemia and reduce the inflammatory response [27], improve protein balance [30] and wound healing [31].

However, the glycemic control in patients that need intensive care can lead to hypoglycemic episodes [8,11,32]. Important to highlight that normal glycemic level in humans is considered to be between 80-110 mg/dl [33]. Patients with hypoglycemia (blood glucose <60 mg/dl) have many negative effects similar to hyperglycemia (blood glucose >110 mg/dl), for example, increased inflammatory and metabolic responses, frequent infections, tendency to multiple organ failure and rise in mortality [9].

Jeschke and collaborators [34] found that IIT for severely burned children maintained stable glucose levels and significantly improved insulin sensitivity. Effective glucose control attenuated a hypermetabolic response compared to patients with ineffective glucose control. However, sometimes glycemic control with insulin therapy resulted in these patients experiencing several episodes of hypoglycemia.

Fram *et al.* [35] demonstrated that children with burned total body surface area  $\geq 40\%$  who received IIT maintained daily blood glucose levels between 80 - 110 mg/dl, but those children who received conventional insulin therapy maintained blood glucose levels  $\geq 215$  mg/dl. The authors observed in burned children with control glucose levels  $\leq 120$  mg/dl improved insulin sensitivity, and decreased oxidative mitochondria and energy expenditure. Tuvdendorj *et al.* [31], in a study with patients <18 years with burned  $\geq 30\%$  total body surface area (TBSA) that received IIT and skin grafting, described there was an increase in the fractional synthesis rate of site wound protein compared to children that did not received any insulin treatment.

It is possible to observe some beneficial effects of intensive insulin therapy and effective glycemic control. However, the challenge related to preventing hypoglycemia episodes persists and needs more research [29]. Due to different glucose levels registered in studies and in numerous protocols related to appropriate insulin dosage, experimental models has been studied as a model of treatment in extensive burns.

Only few studies have proposed systemic therapies for extensive BI. Part of these were experimental studies that used food replacement therapies but hormone treatment are little explored. For this reason, the understanding of hormonal effects as a therapeutic option is an eminent challenge for advances in this field. Therefore, the main criteria for the present paper was to review the literature concerning IIT following scalding injury (SI) in animal models.

**Table 1** Studies that utilized insulin treatment in burn animal models for a minimum of 24 hours (1 day).

Author	TBSA (%)	Insulin/acti on	Via	Dosage	Period of IIT until euthanasia	Results about glycemic control*	Other results of IIT about SI
Emanuele <i>et al.</i> , 2007 [53]	13-15%	Insulin Glargine - Long-acting	Subcutaneous	Once a day, 5UI/kg	Groups with IIT for 1, 2 and 7 days	C < SI > SI+I Had difference between the groups after IIT	IIT decreased liver fatty infiltration and alanine aminotransferase blood levels
Solomon <i>et al.</i> , 2000 [44]	15-20%	Intermediate -acting insulin	Subcutaneous	Twice a day (11-12h intervals), dose was gradually increased	0.25U (day 1 and 2), 0.5U (day 3), 1.0U (day 4)/100g. Groups with IIT for 1 and 4 days	IIT did not induce long-term hypoglycemia, in 3h glycemia returned to normal values.	IIT suppressed of ubiquitin conjugation to endogenous proteins and cathepsin activities
Solomon <i>et al.</i> , 2002 [45]	15-20%	Intermediate -acting insulin	Subcutaneous	Twice a day (11-12h intervals), dose was gradually increased	0.25U (day 1 and 2), 0.5U (day 3), 1.0U (day 4)/100g. Groups with IIT for 4 days	IIT did not induce long-term hypoglycemia, in 3h glycemia returned to normal values.	IIT restored body weight by reducing protein degradation and regaining the intracellular protein content in skeletal muscle
Madibally <i>et al.</i> , 2003 [15]	15-20%	Intermediate -acting insulin	Subcutaneous	Twice a day (11-12h intervals), dose was gradually increased	0.25U (day 1 and 2), 0.5U (day 3), 1.0U (day 4)/100g. Groups with IIT for 4 and 15 days	IIT did not induce long-term hypoglycemia, in 3h glycemia returned to normal values.	IIT decreased inflammatory cells and increased vasodilation, reepithelialization, collagen deposition in wounds burn skin
Madihally <i>et al.</i> , 2006 [46]	15-20%	Intermediate -acting insulin	Oral	Twice a day (11-12h intervals), dose was gradually increased	Insulin particles were loaded into gelatin capsules for oral administration. 0.25U (day 1), 0.5U (day 2), 1.0U (day 3)/100g. Groups with IIT for 15 days	IIT did not induce long-term hypoglycemia, in 3h glycemia returned to normal values.	IIT improved the body weight gain of burned rats and accelerated the wound healing
Jeschke <i>et al.</i> , 2002 [38]	30%	Protamin insulin - Long-acting	Subcutaneous	Once a day, 5UI/kg	Groups with IIT for 1, 2, 5 and 7 days	C < SI > SI+I Had significant difference between the groups after IIT	IIT attenuated the inflammatory response by decreasing the proinflammatory and increasing the anti-inflammatory cascade in serum blood
Klein <i>et al.</i> , 2004 [39]	30%	Protamin insulin - Long-acting	Subcutaneous	Once a day, 5UI/kg	Groups with IIT for 1, 2, 5 and 7 days	SI > SI+I Had significant difference between the groups after IIT	IIT decreased the expression of pro-inflammatory cytokines mRNA and apoptosis in the liver

Zhang <i>et al.</i> , 2011 [48]	30%	-	Subcutaneous	Once a day, 3 to 5UI/kg	Groups with IIT for 24 hours	C $\cong$ SI+I < SI IIT did not induce hypoglycemia. Had significant difference between SI+I and SI groups, for 3, 6, 12 and 24h after IIT	IIT decreased pulmonary edema, hemorrhage, inflammatory cell infiltration and apoptosis
Wang <i>et al.</i> , 2012 [41]	30%	Insulin Glargine - Long-acting	Intraperitoneally	Once a day, glucose-insulin (70UI <sup>-1</sup> ) and insulin 30UI <sup>-1</sup>	Groups with IIT for 1, 3 and 5 days	SI+I < SI $\cong$ SI+GI** Had significant difference between the groups after IIT	IIT attenuated the inflammation and necrosis on the intestinal epithelium
Han <i>et al.</i> , 2014 [49]	30%	-	Subcutaneous	Once a day, 3 to 5UI/kg	Groups with IIT for 24 hours	C $\cong$ SI+I < SI IIT did not induce hypoglycemia. Had significant difference between SI+I and SI groups, for 3, 6, 12 and 24h after IIT	IIT attenuated the increase of pulmonary endothelial permeability and decreased pulmonary edema, hemorrhage, inflammatory cell infiltration and apoptosis
Przkora <i>et al.</i> , 2007 [47]	35%	Intermediate-acting insulin	Intraperitoneally	Once a day, 5UI/Kg	Group with IIT for 5 days	SI+I $\cong$ SI	IIT decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines in serum blood, increasing survival to <i>Pseudomonas aeruginosa</i>
Pidcoke <i>et al.</i> , 2014 [40]	40%	Protamin zinc insulin - Long-acting	Subcutaneous	Once a day, 5UI/Kg	Group with IIT for 12 days	Glucose tolerance test C $\cong$ SI+I < SI Had significant difference between the groups	IIT attenuated the hypermetabolic response and atrophy muscle
Gauglitz <i>et al.</i> , 2010 [42]	60%	Insulin Glargine - Long-acting	Subcutaneous	Once a day, dose was gradually increased	1U (day 1), 2,5U (day 2), 5U (day 3)/100g. Groups with IIT for 28 days	C $\cong$ SI+I < SI Had significant difference between SI+I and SI groups, for 3 and 6h after IIT	IIT attenuated acute pro-inflammatory response, increasing survival to <i>Pseudomonas aeruginosa</i> burn wound infection
Jeschke <i>et al.</i> , 2010 [43]	60%	Insulin Glargine - Long-acting	Subcutaneous	Once a day, 2.5 UI/kg	Group with IIT for 1 and 2 days	C $\cong$ SI+I < SI Had significant difference between the groups	IIT decreases hepatic apoptosis, mitochondrial damage, and increases albumin production

\*To facilitate the understanding of the reader, we will call here the groups of the revised papers: Control for sham animals without IIT and without SI; SI for the injured group without IIT; and SI+I for injured and treated groups.

\*\*Only this paper presented a SI group with treatment mixed insulin (IIT) and glucose (SI+GI)

### 3.3. Intensive insulin therapy in experimental models of extensive burn injury

The extent of the SI varied greatly between articles (13-60%). SI of 30% TBSA or more was considered extensive and resulted in hormonal and metabolic, local and systemic responses [4, 5, 10, 36]. However, all articles presented in Table 1 indicated several systemic responses in many body organs or systems, independent of the TBSA scald burn.

The periods of IIT in the papers studied changed considerably. Some focused on short-term treatments between 1 and 5 days, regardless of the type of insulin used or daily doses defined. However, only two articles focused on 7-day treatments to evaluate the long term infiltration of adipose tissue into the liver [37] and the decrease of several pro-inflammatory markers [38]. Finally, just one paper lasted 15 days, until the complete regeneration of the animals' skin wounds.

Seven of the fourteen papers (Table 1) mentioned the use of long-acting insulin for IIT; three used protamine insulin [38-40] and four used glargine insulin [37, 41-43]. Five other papers used intermediate-acting insulin [15,44-47]. Two papers [48, 49] did not report the period of insulin action, but reported that the insulin dose and glucose blood level were controlled daily. Just one paper used a mixture of 5 IU/kg insulin injected together with glucose, once a day [41], in order to avoid hypoglycemia in treated animals.

Insulin glargine and protamine are long-acting types of insulin that reach a plateau of biological action, promoting a basal coverage throughout 24 hours [50, 51]. Studies with humans showed that patients treated with glargine, long-acting insulin, had significantly lower hypoglycemia events compared to patients that use intermediate-acting insulin, such as neutral protamine hagedorn insulin (NPH) [52].

Regarding the dosage of IIT, the groups that applied insulin with a gradual dosage increase from 0.5IU to 1.0IU per 100 g of animal body weight, used two applications per day because they used intermediate-acting insulin that has a half-life of between 11 and 12 hours [15, 44-46]. The similar dosage was applied in the groups that received long-acting insulin (2.5 to 5 IU / kg), but only a daily dosage was applied [38-40, 43, 48, 49, 53]. Just a paper utilized intermediate-acting insulin in a daily dosage [47]. Related to the insulin routes of administration form, only Medihally et al. [46] used oral insulin, the other authors applied intraperitoneal or subcutaneous injections.

Regarding the insulin action, the number of daily injections was once when the authors used a long-acting insulin, and two for intermediate-acting insulin. This latter insulin type required an increase of animal manipulation and consequently this animal receive more stress than the animal that received double subcutaneous injections, except for assays presented by Przkora et al. [47] who injected the intermediate-acting insulin once a day. Then, a long-acting insulin therapy would minimize the stress and manipulation of animals that already have the injury burn stress.

Among the factors that provided influence in experimental models with IIT, the most important was the glyceimic control. In experimental models with extensive SI, the rats or mice had an acute state of hyperglycemia that was maintained in few days after SI. Hyperglycemia and hypermetabolism cause metabolic stress, which is the most significant response to SI [6, 42], as result of increased hepatic gluconeogenesis [6].

In the surveyed papers, the glyceimic control was carried out daily in all animals that received the treatment because of IIT and the glyceimic changes promoted by extensive SI. Thus, the blood glucose level evaluations showed that the animals' glyceimia returned to normal values approximately 3 hours after IIT, indicating that IIT does not induce long-term hypoglycemia [44, 46]. However, in studies that administered a gradually increasing IIT dose, the animals had hypoglycemia in the first hour after insulin administration (1U/100g) [44, 45]. That indicated that the dosage was too high for these animals. Interestingly, just one study used a fourth group for comparing parameters of glyceimia and insulinemia control. The sham group received ITT the same as the SI group [45].

For studies that use hormone therapy with insulin, an important consideration is regard to glyceimic control because the risk of hypoglycemia [7, 54]. Therefore, all the reviewed papers focused on glyceimic control of the animals, one hour or a few days after starting IIT, or at the end of IIT.

In the initial phase of the response to the extensive SI, a hyperglycemic state occurs, followed by a subsequent phase where there was predominance of protein hypermetabolism [6]. Thus, some studies consider that insulin did not induce long periods of hypoglycemia after IIT, regardless of the dosage injected. Approximately 3 hours after application, the animals were euglycemic [15, 44-46]. So, IIT with exogenous insulin has been shown capable of reducing hyperglycemia, together with the level of IR [54]. In the surveyed papers, the animals submitted to extensive SI showed

hyperglycemia in the evaluation of glycemic control, compared to the Control and SI+IIT groups. Therefore, insulin was able to revert the hyperglycemia after SI, regardless of the dosage administered, number of daily applications, type of insulin (intermediate or long action) and, number of days of treatment [38,39,41,43,47–49,53,55].

In addition to the glycemic control results, the IIT also was able to promote systemic responses linked to the consequences of extensive SI that the animals received. Other effects of IIT were observed in wound healing, several organs, such as liver, skeletal muscle, lung and intestine, and investigated in inflammatory cascades in blood.

IIT induced wound healing. Four days after SI, in the acute phase, a histologic evaluation of SI wounds showed decrease of inflammatory cells, and increase in vasodilation and collagen deposition. In a late phase, after 15 days, IIT increased re-epithelization when compared to SI untreated group [15]. The acceleration of wound healing in animals that received IIT also promoted body weight gain [46].

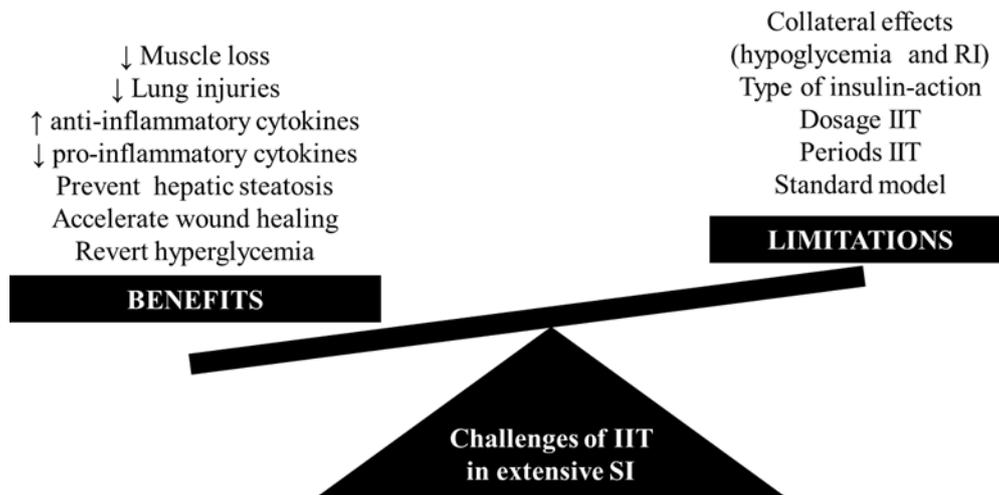
Regarding the liver, IIT decreased hepatic apoptosis, mitochondrial damage, and increased albumin production in acute phase, at 24 and 48 hours, after SI [43]. Seven days after SI, in the late phase, IIT decreased blood levels of alanine aminotransferase enzyme, related to damage to hepatocytes membrane. In addition, it prevented an increase of microvesicular steatosis [53], and decreased the mRNA expression of some pro-inflammatory cytokines [39].

IIT markedly attenuated acute lung injuries. In histologic analyses of lungs, a decrease has been observed in pulmonary edema, haemorrhages, inflammatory cell infiltration and cell apoptosis after 12 hours [48,49] and 24 hours [48], besides attenuating the increase of pulmonary endothelial permeability induced by BI [49]. Finally, Wang et al. [41] investigated the effects of SI on the intestine and used IIT together with glucose. After 2 days of treatment, the animals showed a decrease in infiltration of inflammatory cells and necrosis sites in intestinal epithelium compared to the untreated SI group.

IIT has been found to suppress the ubiquitin conjugation of endogenous proteins in muscle, and to decrease some cathepsin activities after 1 and 4 days [44], and also to restore body weight by reducing accelerated protein degradation after 4 days [45]. In animals that have been submitted to SI and had their limbs immobilized, IIT attenuated the muscle loss in soleus and gastrocnemius muscles, the hypermetabolic response and atrophy. It also increased glucose clearance and normalized circadian-metabolic protein [40].

Regarding of SIRS the extensive SI, IIT was also capable of reducing the inflammation after 1 to 7 days, by decreasing several pro-inflammatory cytokines (TNF, IL-1 and IL-6), and increasing anti-inflammatory cytokines (IL-2, IL-4 and IL-10) in blood serum [45]. The application of IIT together with glucose after 1 to 5 days decreased the IL-10 and TNF expression [41]. One of the most common bacteria that cause lethal infections in burn patients is *Pseudomonas Aeruginosa*. In animals that received an injection of these bacteria after SI, IIT was capable of decreasing several pro-inflammatory cytokines and increasing several anti-inflammatory cytokines in serum blood in these animals [47]. IIT also improved the survival of the animals following infection of SI wounds with *Pseudomonas Aeruginosa* [42]. Summering IIT has been shown as effective therapy for the care of systemic effects post extensive BI.

The variations of treatment and difficulties related to obtaining invasive analysis of tissues in humans and appropriate glucose levels without hypoglycemic episodes during the treatment, justify the importance of experimental study in this area. In experimental models, IIT has been shown as capable of improving glycemic control and attenuate numerous disturbs caused by SI. However, it is important to highlight that the extension of lesion, periods of IIT, type and dosage of insulin varied considerably. Thus, Figure 2 presents the benefits and limitations of the IIT of extensive SI models in a schematic form on a scale. In addition, there are difficulties to establish the ideal glucose level to consider normoglycemic state of varieties of species utilized. The main challenge consists in establish the gold standard of glucose level associated to the attenuation of as much as possible systemic effects of SI. So more studies about results of treatments in humans and standardized experimental models are necessary to the best knowledge of insulin treatment post extensive burn.



**Figure 2** Benefits and limitations of ITT of extensive SI models. Note that although there are limitations based on burn standard or insulin administration, numerous benefits of systemic effects attenuation post SI are considered.

#### 4. Conclusion

It concludes, although there are limitations related to burn standard or insulin administration, the systemic benefits effects of ITT outweigh limitations.

#### Compliance with ethical standards

##### *Acknowledgments*

We would like to thank anonymous reviewers for constructive comments on the manuscript.

##### *Disclosure of conflict of interest*

The authors declare no conflict of interest. And all authors have made substantial contributions to the article.

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#### How to cite this article

Quintana HT, Baptista VIA, Lazzarin MC and De Oliveira F. (2020). Challenges of the intensive insulin therapy in experimental models of extensive burn injury. *World Journal of Advanced Research and Reviews*, 7(2), 34-44.

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