Glisemik Kontrol

Prof. Dr. Koray Topgül

İstanbul Kemerburgaz Üniversitesi TF Genel Cerrahi AD

- Çıkar çatışmam yoktur.

The New England
Journal of Medicine

VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Study Design

At the time of admission to the intensive care unit, patients were randomly assigned to receive either intensive or conventional insulin therapy. Assignments to the treatment groups were made with the use of sealed envelopes, with stratification according to the type of critical illness (Table 1), and were balanced with the use of permuted blocks of 10. In the conventional-treatment group, a continuous infusion of insulin (50 IU of Actrapid HM [Novo Nordisk, Copenhagen, Denmark] in 50 ml of 0.9 percent sodium chloride), with the use of a pump (Perfusor-FM, B. Braun, Melsungen, Germany), was started only if the blood glucose level exceeded 215 mg per deciliter,[8,9] and the infusion was adjusted to maintain the level at a value between 180 and 200 mg per deciliter (10.0 and 11.1 mmol per liter).

In the intensive-treatment group, an insulin infusion was started if the blood glucose level exceeded 110 mg per deciliter, and the infusion was adjusted to maintain normoglycemia (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]). The maximal dose of insulin was arbitrarily set at 50 IU per hour. When the patient was discharged from the intensive care unit, a conventional approach was adopted (maintenance of blood glucose at a level between 180 and 200 mg per deciliter).

TABLE 3. MORTALITY.

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
Reason for intensive care			
Cardiac surgery	25/493 (5.1)	10/477 (2.1)	
Neurologic disease, cerebral trauma, or brain surgery	7/30 (23.3)	6/33 (18.2)	
Thoracic surgery, respiratory insufficiency, or both	10/56 (17.9)	5/66 (7.6)	
Abdominal surgery or peritonitis	9/58 (15.5)	6/45 (13.3)	
Vascular surgery	2/32 (6.2)	2/30 (6.7)	
Multiple trauma or severe burns	3/35 (8.6)	4/33 (12.1)	
Transplantation	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	
No history of diabetes	57/680 (8.4)	31/664 (4.7)	
No history of diabetes and >5 days of intensive care	45/218 (20.6)	20/187 (10.7)	
History of diabetes	6/103 (5.8)	4/101 (4.0)	
History of diabetes and >5 days of intensive care	4/25 (16.0)	2/21 (9.5)	
Cause of death — no.			0.02
Multiple-organ failure with proven septic focus	33	8	
Multiple-organ failure without detectable septic focus	18	14	
Severe brain damage	5	3	
Acute cardiovascular collapse	7	10	
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

*P values were determined with the use of the chi-square test. For the primary outcome variable (death during intensive care), the P value has been corrected for the repeated interim analyses, according to the method of Lan and DeMets[30]; the unadjusted P value is 0.005. Sequential interim analyses were not performed for the other variables, and nominal (unadjusted) P values are given for these comparisons.

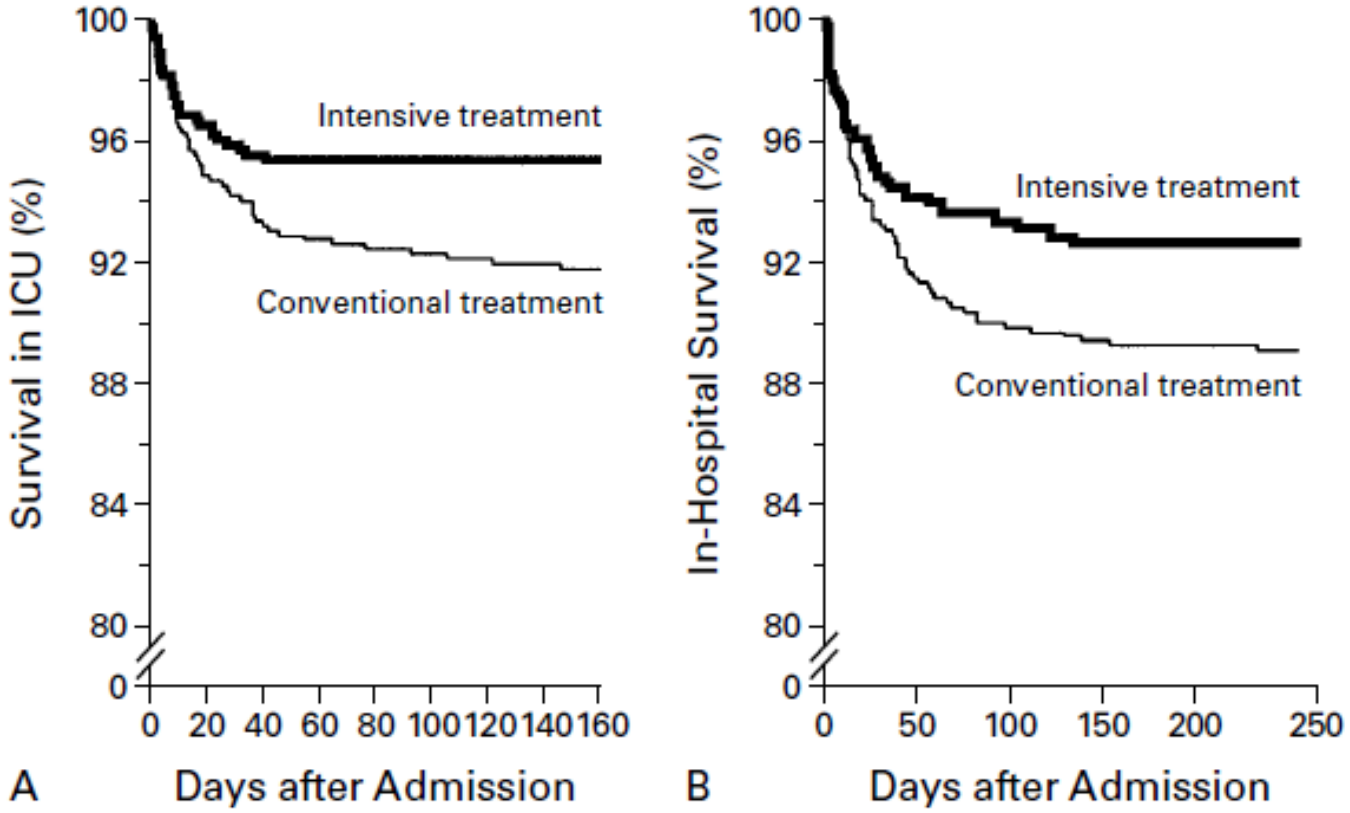


Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).

Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal $P=0.005$ and adjusted $P<0.04$; in-hospital survival, nominal $P=0.01$). P values were determined with the use of the Mantel–Cox log-rank test.

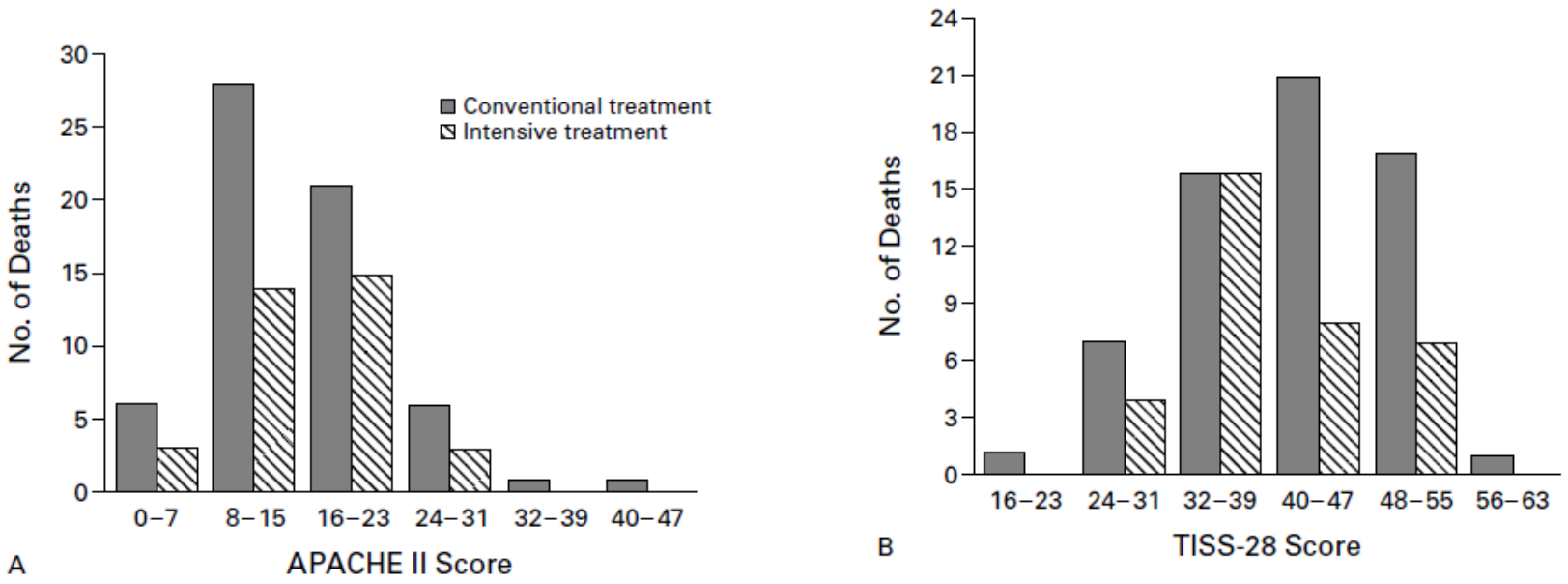


Figure 2. Number of Deaths in the Intensive Care Unit According to the Acute Physiology and Chronic Health Evaluation (APACHE II) Score (Panel A) and the Simplified Therapeutic Intervention Scoring System (TISS-28) Score (Panel B) in the First 24 Hours.

Higher APACHE II scores indicate more severe illness, and higher TISS-28 scores indicate a higher number of therapeutic interventions.

TABLE 4. MORBIDITY.*

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE†
Duration of intensive care — days			
All patients			
Median	3	3	0.2
Interquartile range	2–9	2–6	
≤5 Days			
Median	2	2	0.2
Interquartile range	2–3	2–3	
>5 days			
Median	15	12	0.003
Interquartile range	9–27	8–20	
Patients requiring >14 days of intensive care — no. (%)	123 (15.7)	87 (11.4)	0.01
Duration of ventilatory support — days			
All patients			
Median	2	2	0.06
Interquartile range	1–6	1–4	
≤5 Days of intensive care			
Median	1	1	0.9
Interquartile range	1–2	1–2	
>5 Days of intensive care			
Median	12	10	0.006
Interquartile range	7–23	6–16	
Patients requiring >14 days of ventilatory support — no. (%)	93 (11.9)	57 (7.5)	0.003
Inotropic or vasopressor treatment — no. (%)	586 (74.8)	574 (75.0)	0.9
Renal impairment — no. (%)			
Peak plasma creatinine >2.5 mg/dl	96 (12.3)	69 (9.0)	0.04
Peak plasma urea nitrogen >54 mg/dl	88 (11.2)	59 (7.7)	0.02
Dialysis or continuous venovenous hemofiltration	64 (8.2)	37 (4.8)	0.007
Hyperbilirubinemia (peak bilirubin >2 mg/dl) — no. (%)	209 (26.7)	171 (22.4)	0.04
Bloodstream infection — no. (%)			
Septicemia during intensive care	61 (7.8)	32 (4.2)	0.003
Treatment with antibiotics for >10 days	134 (17.1)	086 (11.2)	<0.001
Electromyographic evidence of critical-illness polyneuropathy — no./total no. (%)			
At any time	107/206 (51.9)	45/157 (28.7)	<0.001
On more than 2 occasions	39/206 (18.9)	11/157 (7.0)	0.001
Red-cell transfusions			
Patients requiring transfusion — no. (%)	243 (31.0)	219 (28.6)	0.3
No. of transfusions/patient‡			
Median	2	1	<0.001
Interquartile range	1–3	1–2	
Cumulative TISS-28 score§			
All patients			
Median	108	105	0.2
Interquartile range	76–293	76–215	
≤5 Days of intensive care			
Median	84	85	0.3
Interquartile range	67–111	68–115	
>5 Days of intensive care			
Median	563	431	<0.001
Interquartile range	329–956	271–670	

?

Hiperglisemi Neden Gelişiyor?
(Cerrahi Travmaya Yanıt)

- Stres hormonları *kortizol, katekolaminler* ve *glukagon* (Counter-regulatory hormones) katabolik etkileri ile direk ya da indirek olarak insulin salınımını azaltır ve periferal etkisini bozar.

- Cerrahi sırasında dekstroz içinde dilüe edilen ilaçlar (antibiyotikler, katekolaminler, nitrogliserin) hiperglisemiyi alevlendirir.

- Kan ürünleri yüklü miktarda glukoz içerir.

- İnsülin Direnci!!! Normal konsantrasyonda insüline subnormal biyolojik yanıt.
- Glukoz ürünleri ↑ periferal glukoz kullanımı ↓
- Diyabetik olmayanlarda KŞ 200 mg/dl'ye diyabetiklerde bu 300 mg/dl ye kadar yükselebilir.
- Hipergliseminin boyutu cerrahi travmanın şiddetine bağlıdır!
- Laparoskopik cerrahide açık cerrahiye göre glukoz kullanımı daha iyi ve hiperglisemi riski daha düşük.

- İnsülin direnci en yoğun postoperatif ilk gündür (%70) ve komplike olmayan karın ameliyatları sonrası 3 haftaya kadar uzayabilir.

- İnsülin direnci primer olarak cerrahinin invazivliğine bağlı olsa da travmanın süresi, yatak istirahati ve immobilizasyon, anestezi ve analjezinin tipi, nutrisyon ve perioperatif açlık da etkilemektedir.

- İnhalasyon anestezikleri (isofluran ve sevofluran) glukoz uyarımlı insulin salınımını baskılar.

Pankreas

beyin

immün hücreler

edotelyal hücreler

insuline bağımlı olmadan

glukoz transportunu sağlar.

* *İskelet kası, *kalp kası, *yağ dokusu* ve **karaciğer*

İnsulin bağımlıdır.

Hipergliseminin Yıkıcı Etkileri?

- İmmün fonksiyonları baskılar (kemotaksis, fagositoz, bakterilerin hücre içi öldürülmesi)
- İnflamatuar sitokinleri artırır.
- Nitrik oksid ürünlerini azaltır.
- Anjiyotensin II düzeyini, sistemik damar direncini artırır.
- Ozmotik diüreze neden olur bu da dehidratasyona yol açar.
- Hiperozmolarite SSS de disfonksiyona neden olur, bunu da hızla düzeltilmesi daha kötü ödeme yol açar.

- Nutrisyon: Amaç….. enerji ve protein katabolizmasından korunma

- Hiperglisemi protein katabolizmasını alevlendirebilir.

- Kanserli hastaların major cerrahisi sonrası sonrası PE Nutrisyonla yaratılan hiperglisemi kas protein katabolizmasını artırırken, normoglisemi nötral protein balansını sağlar.

İnsülinin Metabolik Etkileri

- Glukozun özellikle de periferal dolaşımdaki (iskelet kası) tutulumunu artırıp dolaşımdaki glukoz düzeyini azaltır.

- Karaciğerde glikokinazı aktive eder ve endojen glukoz üretimini (primer karaciğer) glukogneogenez ve glikolizisi azaltmak yoluyla düşürür.

İnsülinin Metabolik Olmayan Etkileri

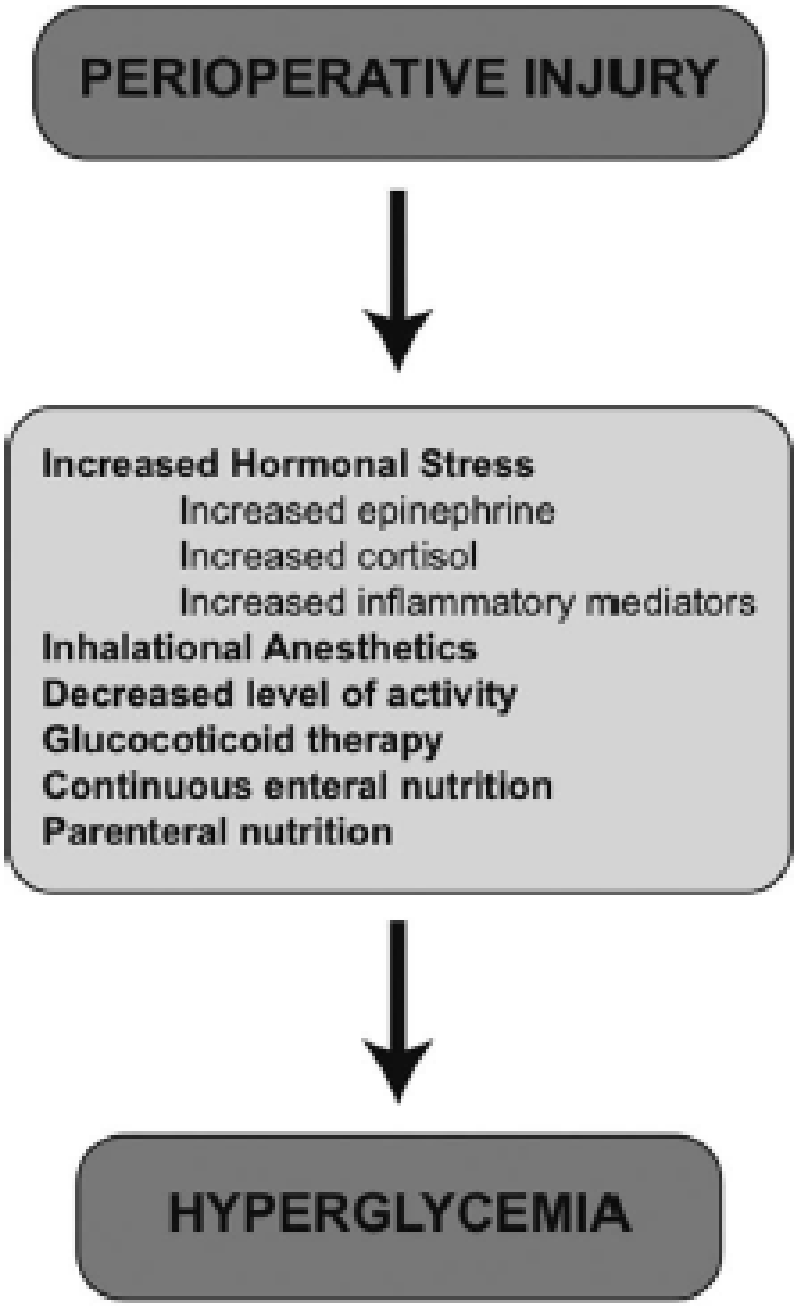
- Bazı proinflamatuar transkripsiyon faktörlerini (nukleer faktör-kB) baskılar ve endotoksin kaynaklı inflamatuar medyatörlerinin (IL-1B, IL-6, makrofaj migrasyon inhibe edici fatör, TNF-a) sunumunu azaltır…ANTİİNFLAMATUAR ETKİ

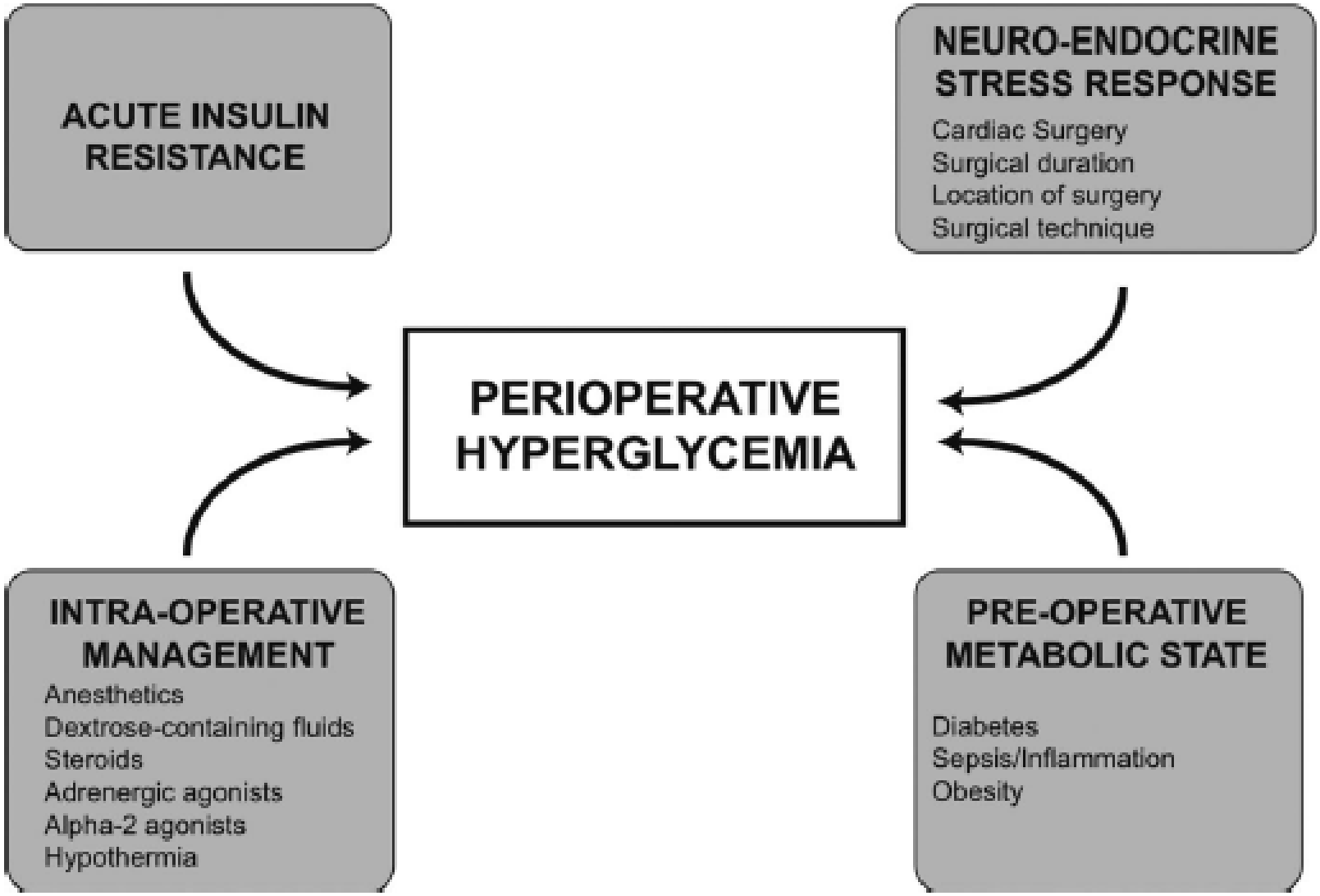
- Antiangregan etki—platelet agregasyonunu inhibe edici ve selektif vazodilatasyon etkisi vardır.
- Doku faktörlerinin, intraselüler adezyon moleküllerini, reaktif oksijen radikallerini,..inhibe ederek antitrombotik, antifibrinolitik ve antioksidan etki gösterir.
- Antiapopitotik özellikleri vardır.

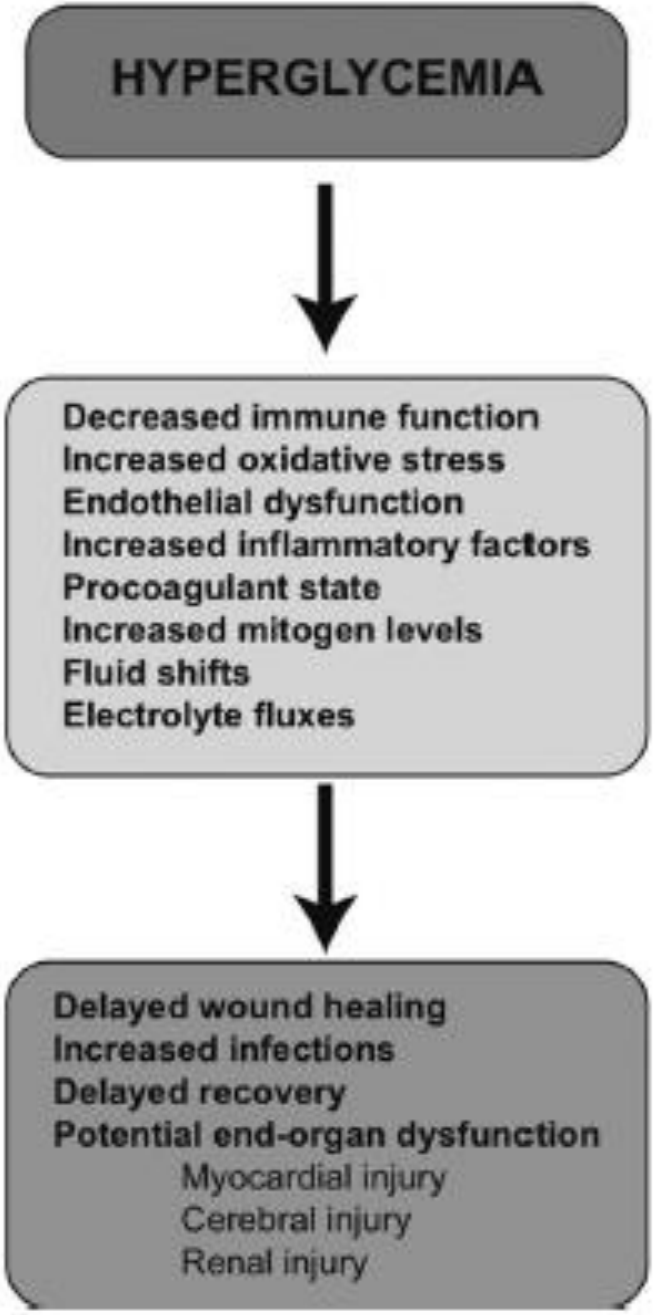
Scientific Principles and Clinical Implications of Perioperative Glucose Regulation and Control

Shamsuddin Akhtar, MBBS* Paul G. Barash, MD* Silvio E. Inzucchi, MD†

ANESTHESIA & ANALGESIA




ACUTE INSULIN RESISTANCE
NEURO-ENDOCRINE STRESS RESPONSE
Cardiac Surgery
Surgical duration
Location of surgery
Surgical technique
PERIOPERATIVE HYPERGLYCEMIA
INTRA-OPERATIVE MANAGEMENT
Anesthetics
Dextrose-containing fluids
Steroids
Adrenergic agonists
Alpha-2 agonists
Hypothermia
PRE-OPERATIVE METABOLIC STATE
Diabetes
Sepsis/Inflammation
Obesity


HYPERGLYCEMIA
Decreased immune function
Increased oxidative stress
Endothelial dysfunction
Increased inflammatory factors
Procoagulant state
Increased mitogen levels
Fluid shifts
Electrolyte fluxes
Delayed wound healing
Increased infections
Delayed recovery
Potential end-organ dysfunction
Myocardial injury
Cerebral injury
Renal injury

Perioperatif/YBÜ hastalarında

- *Hiperglisemi kötüdür*
- *İnsülin iyidir*
- *Sıkı glisemik kontrol yapılmalıdır!!*

The NEW ENGLAND JOURNAL of MEDICINE

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

N Engl J Med 2008;358:125-39.

METHODS

In a multicenter, two-by-two factorial trial, we randomly assigned patients with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES 200/0.5), or modified Ringer's lactate for fluid resuscitation. The rate of death at 28 days and the mean score for organ failure were coprimary end points.

RESULTS

The trial was stopped early for safety reasons. Among 537 patients who could be evaluated, the mean morning blood glucose level was lower in the intensive-therapy group (112 mg per deciliter [6.2 mmol per liter]) than in the conventional-therapy group (151 mg per deciliter [8.4 mmol per liter], $P<0.001$). However, at 28 days, there was no significant difference between the two groups in the rate of death or the mean score for organ failure. The rate of severe hypoglycemia (glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was higher in the intensive-therapy group than in the conventional-therapy group (17.0% vs. 4.1%, $P<0.001$), as was the rate of serious adverse events (10.9% vs. 5.2%, $P=0.01$). HES therapy was associated with higher rates of acute renal failure and renal-replacement therapy than was Ringer's lactate.

CONCLUSIONS

The use of intensive insulin therapy placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycemia. As used in this study, HES was harmful, and its toxicity increased with accumulating doses. (ClinicalTrials.gov number, NCT00135473.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2009 VOL. 360 NO. 13

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

BACKGROUND

The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS

Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). We defined the primary end point as death from any cause within 90 days after randomization.

RESULTS

Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P=0.10). Severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (P=0.84) or hospital (P=0.86) or the median number of days of mechanical ventilation (P=0.56) or renal-replacement therapy (P=0.39).

CONCLUSIONS

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)

Severe hypoglycemia in critically ill patients: Risk factors and outcomes*

James S. Krinsley, MD, FCCM, FCCP; Aarti Grover, MD

Crit Care Med 2007 Vol. 35, No. 10

Table 3. Multivariate logistic regression analysis: Risk of severe hypoglycemia and mortality

	Severe Hypoglycemia		Mortality	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Diabetes	3.07 (2.03–4.63)	<.0001	0.97 (0.79–1.20)	NS
Septic shock	2.03 (1.19–3.48)	.0096	1.33 (0.98–1.81)	NS
Serum creatinine ≥3 mg/dL	1.10 (0.68–1.77)	NS	1.30 (1.04–1.62)	.0204
Mechanical ventilation	2.11 (1.28–3.48)	.0032	2.43 (2.00–2.95)	<.0001
Treatment in TGC period	1.59 (1.05–2.41)	.0279	0.67 (0.56–0.80)	<.0001
APACHE II (modified)	1.07 (1.05–1.10)	<.0001	1.14 (1.13–1.16)	<.0001
Age	1.01 (0.99–1.02)	NS	1.03 (1.03–1.04)	<.0001
Severe hypoglycemia	N/A	N/A	2.28 (1.41–3.70)	.0008

OR, odds ratio; CI, confidence interval; NS, not significant; TGC, tight glycemic control; APACHE, Acute Physiology and Chronic Health Evaluation.

CONCLUSIONS

This report, reviewing the experience of a large cohort of patients admitted consecutively to an adult medical-surgical ICU, identified diabetes, an admitting diagnosis to the ICU of septic shock, serum creatinine >3 mg/dL, mechanical ventilation, treatment during the TGC period, and severity of illness (as manifested by APACHE II score modified with the age component deleted) as risk factors for the development of severe hypoglycemia, and demonstrated that even a single episode of severe hypoglycemia conferred an increased risk of mortality. The net benefit of intensive insulin therapy, however, far exceeded its deleterious effect. It is likely that safer implementation of TGC will accrue following development of new technologies to monitor glycemic levels, perhaps on a continuous basis (30, 31). Such advances should offer the promise of more widespread and successful implementation of this therapy.

HİPOGLİSEMİ!!!

- Hipoglisemi agresif ve hızlı tedavi edilen hiperglisemi sonucu ve özellikle de sıkı glukoz kontrolü arzulandığında ortaya çıkan bir komplikasyondur.

- YBU deki hastalarda yapılan çalışmalarda sıkı glisemik kontrol yapılanlarda %5.1-25.3 oranında ciddi hipoglisemi (<40mg/dl) saptanmıştır. Hipoglisemi bu grup hastada 3-13 kez daha sıktır.

Vriesendorp TM, et al. Eur J Vasc Endovasc Surg 2004
Brunkhorst FM, et al. N Engl J Med 2008
Van den Berghe G, et al. N Engl J Med 2006

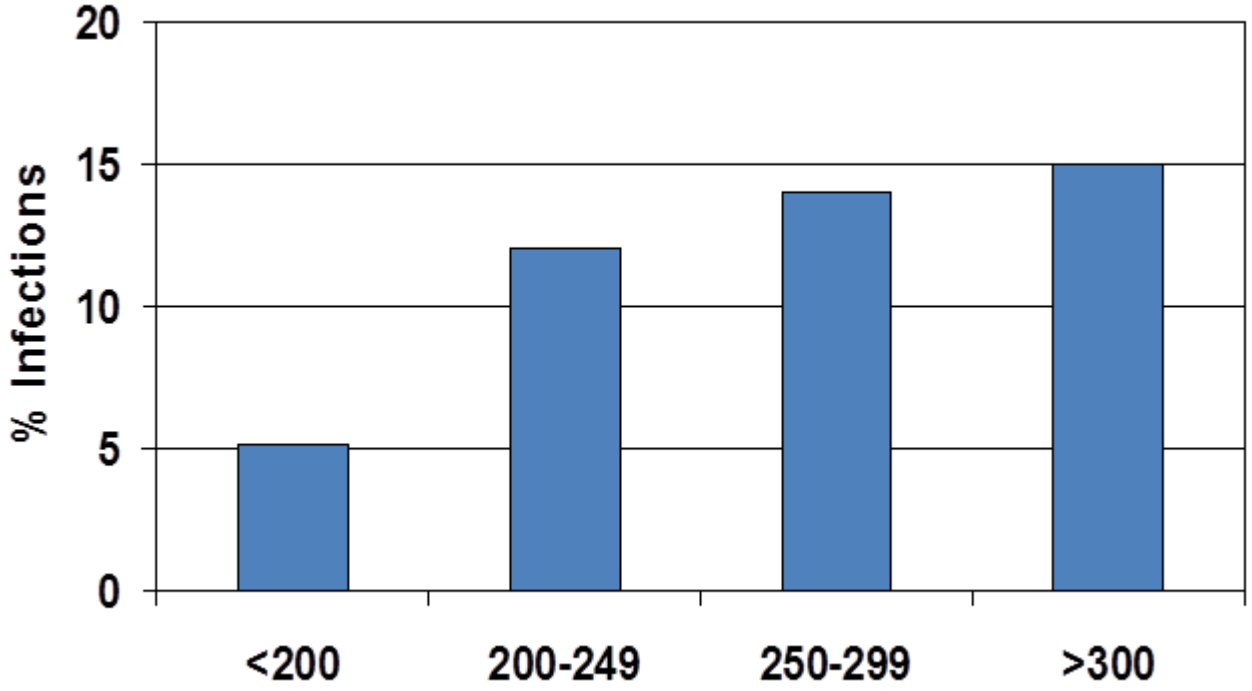
- YBU hastalarında hipoglisemi gelişen hastalarda mortalite insidansı daha yüksektir.

- YBU hastalarında ya da peroperatif hastalarda hipoglisemi semptomları maskelenir, anlaşılmaz.

- İskemik beyin anaerobik metabolizmaya döner ve laktatı enerji kaynağı olarak kullanır. Glukoz seviyelerinde ani düşme iskemik beyine laktat desteğini de düşürerek hasarı artırabilir. Böylece tanınmamış hipoglisemi kötü sonuçlara ve artmış mortalite oranlarına neden olabilir.

McCormick MT, et al. Stroke 2008
Lacherade JC, et al. Intensive Care Med 2007
Nasraway SA Jr. Et al. Crit Care Med 2007
Krinsley JS, et al. Crit Care Med 2007

The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients.
Latham. ICHE 2001; 22: 607-12



- Diyabet ve postoperatif hiperglisemi CAE gelişimi için bağımsız risk faktörüdür.

- Bilinen diyabetlilerde yükselmiş hemoglobin A1c değerleri enfeksiyon riskini artırmaz.

Sonuç:

- Postoperatif hiperglisemi ve önceden tanı almamış diyabet, kardiyotorasik cerrahi geçiren hastalarda artmış CAE riski bulundurmaktadır.

- Diyabet ve hiperglisemi açısından kardiyotorasik cerrahi geçiren hastaların taranması bu metabolik anormalliğin yol açacağı postoperatif ve kronik komplikasyonlardan korunmak için garanti olabilir.

Glucose Control Lowers the Risk of Wound Infection in Diabetics After Open Heart Operations

Kathryn J. Zerr, MBA, Anthony P. Furnary, MD, Gary L. Grunkemeier, PhD, Stephen Bookin, MD, Vivek Kanhere, MD, and Albert Starr, MD

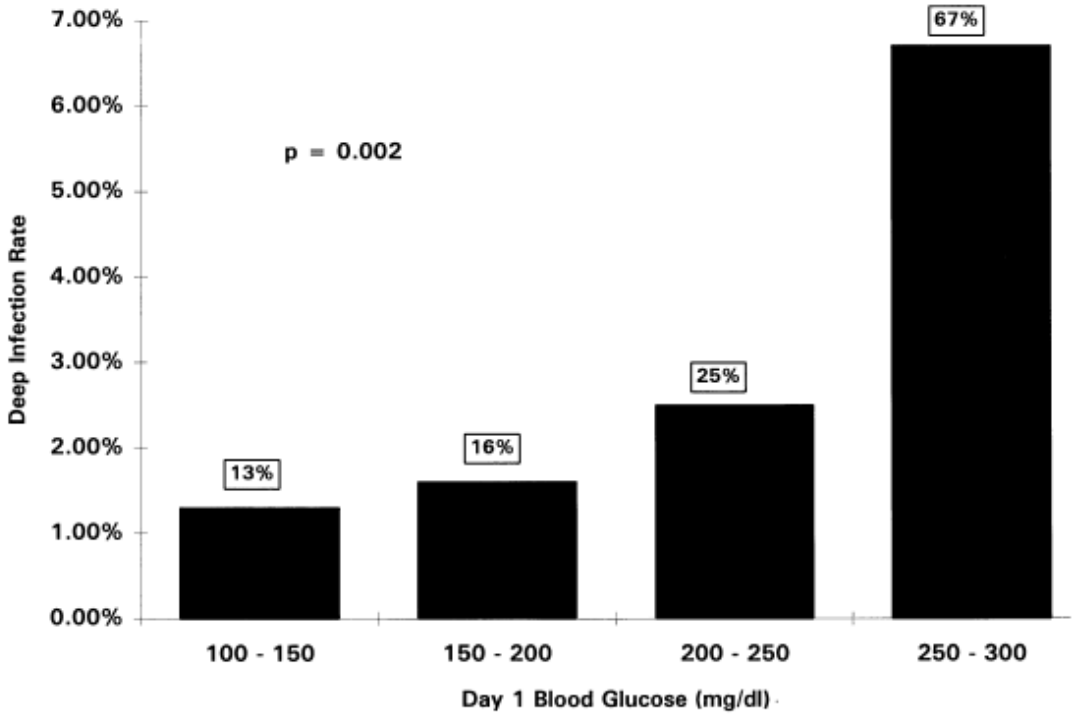


Fig 5. Significant direct relation shown between postoperative blood glucose level and deep infection rates.

Diabetes Care 2014 Nov;37(11):2960-5.

Comparison of glycemic and surgical outcomes after change in glycemic targets in cardiac surgery patients.

Mulla I, Schmidt K, Cashy J, Wallia A, Andrei AC, Johnson Oakes D, Aleppo G, Li C, Grady KL, McGee E, Molitch ME.

OBJECTIVE:

To compare perioperative glycemic and long-term surgical outcomes in patients undergoing cardiac surgery before and after the recommended 2009 changes in inpatient glycemic targets.

RESEARCH DESIGN AND METHODS:

We performed a retrospective review of patients who underwent cardiac surgery between 4 September 2007 and 30 April 2011. Comparison was made of blood glucose (BG) outcomes 3 days after surgery, and 30-day cardiac outcomes before and after a change in insulin protocol that took place on 1 September 2009, which consisted of raising the glycemic targets during intravenous insulin infusions from 80-110 mg/dL (80-110 group) to 110-140 mg/dL (110-140 group).

RESULTS:

When compared with the 80-110 group (n = 667), the 110-140 group (n = 658) had higher mean postoperative BG levels during the intravenous insulin infusion (141 ± 15 vs. 121 ± 15 mg/dL, $P < 0.001$) and the subcutaneous insulin period (134 ± 24 vs. 130 ± 23 mg/dL, $P < 0.001$), and for 3 days postoperatively (141 ± 17 vs. 127 ± 15 mg/dL, $P < 0.001$). Fewer patients in the 110-140 mg/dL group experienced moderate hypoglycemia (BG <70 mg/dL) (177 vs. 73, $P = 0.04$). Severe hypoglycemia (BG <40 mg/dL) occurred in only one patient in the 80-110 group and three patients in the 110-140 group. There were no significant differences in mortality or surgical complication rates (with the exception of reintubation) between the groups.

CONCLUSIONS:

The higher glycemic target of 110-140 mg/dL resulted in similar mean glucose values, with significantly less hypoglycemia and no significant differences in mortality/morbidity compared with the more strict target of 80-110 mg/dL.

*Diyabet durumuna bakılmaksızın perioperatif hiperglisemi (>200 mg/dl) kötü sonuçlarla tamamen ilişkilidir.

Noordzij PG, et al. Eur J Endocrinol 2007

Yendamuri S, et al. J Trauma 2003

Dronge AS, et al. Arch Surg 2006

*409 hasta, retrospektif, kalp cerrahisi..110 mg/dl üzerindeki kan glukoz seviyelerinde her 20 mg/dl'lik artış istenmeyen sonuç riskini %30 artırmaktadır.

Gandhi GY, et al. Mayo Clin Proc 2005

*İnfrainguinal vaskuler cerrahi sonrası retrospektif analiz..postoperatif hiperglisemi artmış postoperatif enfeksiyon nedeni.

Vriesendorp TM, et al. Eur J Vasc Endovasc Surg. 2004

* Randomize çalışma… 78 hasta… Serebral anevrizma nedeniyle subaraknoid kanama geçiren hastalarda klipsleme sonrası sıkı glisemik kontrol grubunda enfeksiyon oranı düşük. (%42---27'ye) …..vazospazm, nörolojik sonuçlar ve mortalite açısından fark yaratmadan.

Bilotta F, et al. J Neurosurg Anesthesiol. 2007

*Karotik endarterektomi uygulanan 1201 hastada perioperatif hiperglisemisi (>200 mg/dl) olanlarda perop (30 gün) inme, MI ve ölüm riski artmıştır.

McGirt MJ, et al. Neurosurgery 2006

*Prospektif randomize…236 hasta….damar cerrahisi….KŞ devamlı insülin infüzyonu ile 100-150 mg/dl aralığında tutulduğunda kardiyovaskuler olay riski azalmaktadır.

Subramaniam B, et al. Anesthesiology, 2009;110:970–7

Genel Cerrahide CAE

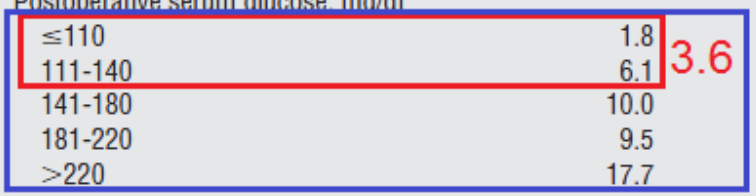
- Genel oran %7.42

- Kolorektal-----%14.11------3.6 kez
- Vaskuler-------%10.32------2.5 kez
- Kolorektal dışı -----%4.36

Ata A, et al. Postoperative Hyperglicemia and Surgical Site Infection in General Surgery, Arch Surg, 2010 (129.909 hasta)

Table 1. Effect of Various Risk Factors on the Odds of Postsurgical Infection in General Surgery Patients

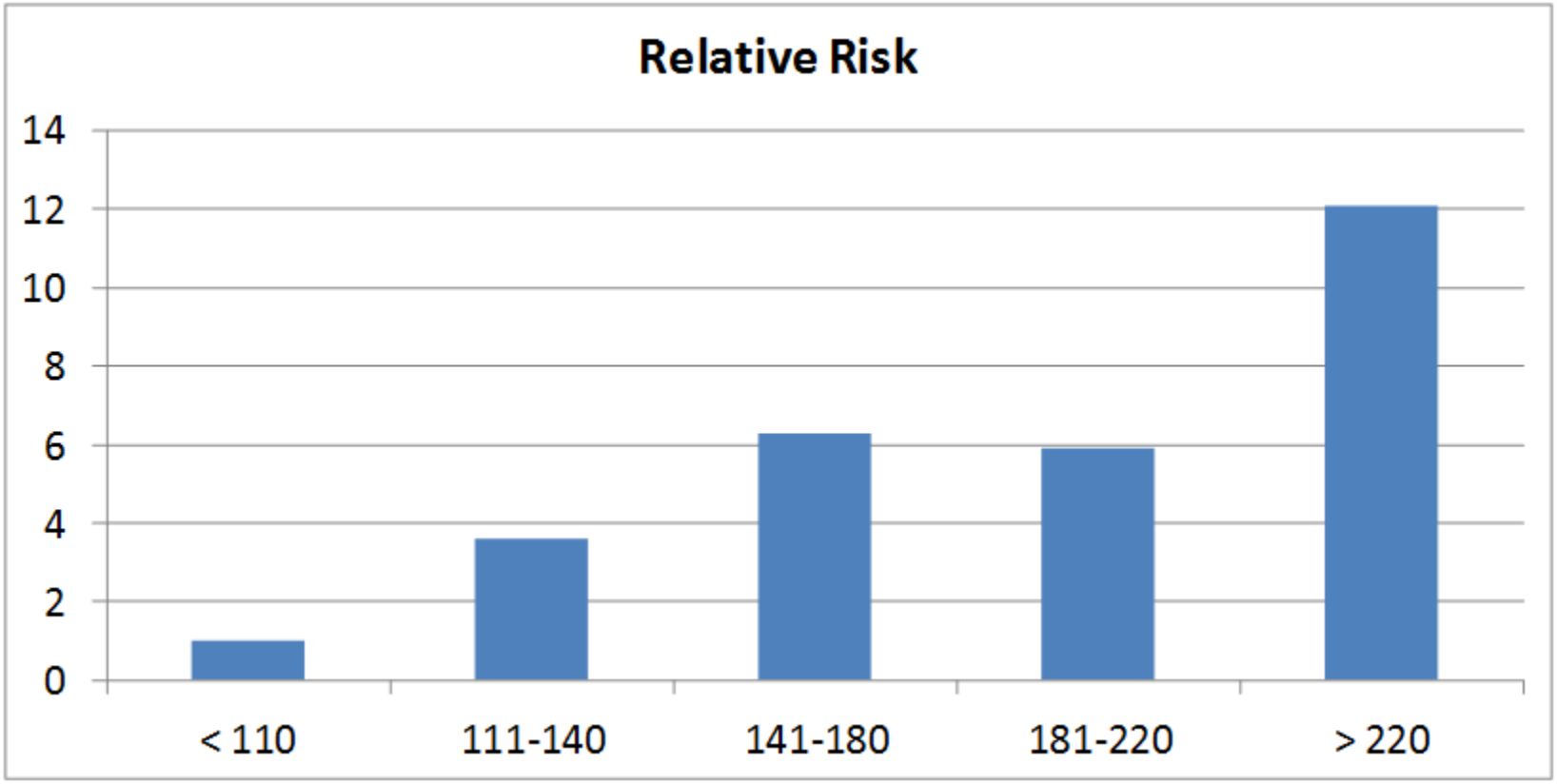
Variable	SSI, %	OR (95% CI)		
		Unadjusted	Adjusted	
			Without Serum Glucose Level	With Serum Glucose Level
Postoperative serum glucose, mg/dl				
≤110	1.8	1 [Reference]	NM	1 [Reference]
111-140	6.1	3.61 (1.22-10.67)	NM	3.61 (1.22-10.67)
141-180	10.0	6.26 (2.17-18.17)	NM	6.26 (2.17-18.17)
181-220	9.5	5.92 (1.73-20.22)	NM	5.92 (1.73-20.22)
>220	17.7	12.13 (3.71-39.64)	NM	12.13 (3.71-39.64)
Age, y				
16-40	3.1	1 [Reference]	1 [Reference]	NM
41-60	5.8	1.91 (1.09-3.33)	1.60 (0.89-2.88)	NM
≥61	8.7	2.95 (1.69-2.12)	2.12 (1.15-3.90)	NM
ASA physical status class				
None to mild (P1/P2)	3.8	1 [Reference]	1 [Reference]	NM
Severe (P3)	6.7	1.80 (1.18-2.74)	1.07 (0.67-1.73)	NM
Life-threatening to moribund (P4/P5)	14.6	4.29 (2.39-7.71)	2.08 (1.07-4.03)	NM
Emergency				
No	5.3	1 [Reference]	1 [Reference]	NM
Yes	9.3	1.84 (1.22-2.80)	2.09 (1.30-3.36)	NM
Operative time[a]		1.05 (1.04-1.07)	1.05 (1.04-1.07)	NM
Diabetes mellitus				
No	5.3	1 [Reference]	1 [Reference]	NM
Yes	11.2	2.26 (1.44-3.55)	1.80 (1.12-2.90)	NM
Preoperative serum glucose, mg/dL				
≤110	5.0	1 [Reference]		
111-140	6.1	1.24 (0.1-2.53)	NM	NM
141-180	5.3	1.08 (0.38-3.12)	NM	NM
181-220	23.3	5.87 (2.38-14.44)	NM	NM
>220	15.4	3.51 (1.16-10.63)	NM	NM
Intraoperative RBC transfusion, U				
≤2	5.7	1 [Reference]	NM	NM
>2	23.5	5.11 (2.26-11.54)	NM	NM



COLORECTAL SURGERY

Subanalysis of colorectal surgery patients in the general surgery group revealed that a postoperative serum glucose level higher than 140 mg/dL was the only significant predictor of SSI for colorectal surgery patients. The incidence of infection in colorectal surgery patients with postoperative serum glucose levels higher than 140 mg/dL (20.6%) was 3.2 times (95% CI, 1.4-7.2 times) that of those with serum glucose levels of 140 mg/dL or less (7.6%).

Postop Glukoz (48 saat) ve CAE



Postoperative Glucose and Mortality in Noncardiac Surgery

- Nondiabetik hastalarda hiperglisemi, diyabetiklerdeki hiperglisemiden daha tehlikelidir!

Frisch. Diabetes Care. 2010; 33: 1883-8

Study	Study type	Number and type of patients	Design	Glycemic goal or range	Salient findings
Postoperative					
Finney et al.[92]	Prospective observational	523 patients, medical (12%), surgical (88%) ICU	Insulin by nonstandardized protocol	90–145 mg/dL	Patients divided into 6 groups. Best outcomes noted in patients with glucose levels between 145 and 180 mg/dL. In all glucose groups, insulin administration was associated with increased risk of death
McAlister et al.[93]	Retrospective	291 patients, CABG	92% received IV insulin by protocol	164–209 mg/dL	Hyperglycemia on POD-1 was an independent predictor of adverse outcomes
Vriesendorp et al.[94]	Retrospective	275 patients, vascular surgery	Nonstandardized protocol	None	Postoperative infection rate correlated with hyperglycemia
Krinsley[95]	Retrospective observational	1600 patients, medical (65%)/ surgical (35%) ICU	Insulin by standardized protocol	<140 mg/dL	Lower incidence of mortality (20.9% vs 14.8%), renal dysfunction (3% vs 12%), and PRBC transfusion (20.5% vs 25.5%). No difference in infection and LOS. No benefit of hyperglycemic control if APACHE score >35
Bochicchio et al.[8]	Prospective observational	942 patients, trauma	Nonstandardized protocol	None	High (glucose > 220 mg/dL), worsening, or highly variable glucose levels associated with increased risk of infection, ICU-LOS, H-LOS, and mortality
Gale et al.[96]	Retrospective	103 patients, trauma ICU	SQ insulin by standardized protocol	<140 mg/dL	Blood glucose level >140 mg/dL was associated with increased morbidity and mortality
Schmeltz et al.[97]	Retrospective	614 patients, cardiothoracic surgery	Insulin by standardized protocol	80–110 mg/dL	Blood glucose level >200 mg/dL on admission to the ICU was associated with increased morbidity and mortality
Reed et al.[98]	Retrospective	7261 patients, trauma	Progressively stringent insulin protocol	Mean glucose decreased from 141 to 129	Decreased incidence of intraabdominal abscesses. Decreased number of days on the ventilator

Prospective Studies

Study	Study type	Number of patients	Study design	Glycemic goal or range	Salient findings
Intraoperative					
Rassias et al.[110]	RCT	30 patients, CABG	Insulin by standardized protocol	75–125 mg/dL	Increased total neutrophil phagocytic capacity in insulin treatment group
Rao et al.[111]	RCT	1127 patients, CABG	Insulin during cardioplegia	None	No difference in myocardial injury and/or low cardiac output syndromes between treatment and control groups
Butterworth et al.[112]	Prospective	381 patients, CABG	Insulin by standardized protocol	<100 mg/dL	No difference in short- and long-term neurological complications between the groups
Koskenkari et al.[113]	RCT	40 patients, CABG + AVR	Insulin by standardized protocol	108–180 mg/dL	Improved myocardial contractile function and decreased inotropic support. No difference in clinical outcomes
Gandhi et al.[107]	RCT	400 patients, CABG	Intraoperative insulin by standardized protocol	80–100 mg/dL	No difference in composite outcomes. Increased number of deaths (4 vs 0) and stroke (8 vs 1) in the intensive insulin group
Postoperative					
van den Berghe et al.[114]	RCT	1548 patients, surgical ICU	Intensive insulin by standardized protocol	<110 mg/dL	Significant difference in morbidity and mortality, in patients who stayed >5 d. No difference in mortality in patients who stayed <5 d (1.7% vs 1.8%)

Grey and Perdrizet[115]	RCT	61 patients, general surgery	Intensive insulin by standardized protocol	80–120 mg/dL	Decrease in nosocomial infection rate
Hoedemaekers et al.[116]	RCT	20 patients, postcardiac surgery	Insulin by standardized protocol	80–110 mg/dL	No difference in outcomes between treatment groups (PRBC transfusion, time on ventilator, ICU-LOS, or renal dysfunction). No difference in IL-10, and IL-6 levels between treatment groups
Bilotta et al.[117]	RCT	78 patients, aneurysm clipping/ neurosurgery	Insulin by standardized protocol	80–120 mg/dL	Infection rate was lower in treatment group. No difference in postoperative vasospasm, neurologic outcome, and mortality rates
Bilotta et al.[118]	RCT	97 patients, traumatic brain injury requiring surgery	Insulin by standardized protocol	80–120 mg/dL	Decreased length of ICU stay. No difference in infection rate and mortality
Bilotta et al.[119]	RCT	483 patients, neurosurgery	Insulin by standardized protocol	80–110 mg/dL	Decreased length of ICU stay and infection rate. No difference in mortality and Glasgow outcome scale at 6 mo
Finfer et al.[11]	RCT	6104 patients, medical/ surgical ICU	Insulin by standardized protocol	81–108 mg/dL	Increased mortality in IGC group. No difference in number of days in the ICU, hospital, on mechanical ventilation, or renal replacement therapy

Yanıtlanmamış Sorular?

1) İntraoperatif ya da postoperatif **hedef değer** ne olmalıdır?

*Kesin bir aralıktan ziyade azaltılmış glisemik değişkenlik daha iyidir.

Ali NA, et al. Crit Care Med 2008

Hirsch IB, et al. J Diabetes Complications 2005

Krinsley JS. Crit Care Med, 2008

*KŞ' deki dalgalanmalar bir takım kötü fizyolojik olayları tetikleyebilir (artmış apopitoz, sitokin sunumunda artış, oksidatif stres).

Fahy BG, et al.Crit Care Med 2009

2)Daha yoğun bir insülin tedavisinin ve sıkı glisemik kontrolün ideal süresi bilinmiyor.

Wilson M, et al. Intensive insulin therapy in critical care: a review of 12 protocols. Diabetes Care 2007

*Furnary ve ark. Portland protokolünü adapte ettikleri çalışmada en az 3 gün IV insülin tedavisi ve sıkı glisemik kontrolü önermekteler. Glisemik kontrol derin sternal yara enfeksiyonunu %66 oranında azaltmaktadır.

Furnary AP, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003

*YBÜ protokolleri yanızca YBÜ'lerinde uygulanmalıdır, süre YBÜ'de kalışlarıyla sınırlanmalıdır. Servise alınan hastalarda monitörizasyon gevşer ve hipoglisemi epizotları gözden kaçabilir!!

Fahy BG, et al. Glucose control in the intensive care unit. Crit Care Med 2009

3) Risk/yarar oranı ---kar/zarar hesabı

Potansiyel yararlarıyla potansiyel zararları eşit değil.

van den Berghe'nin çalışmasında pozitif yönleri öndeyken, NICE-SUGAR çalışmasında sıkı glisemik kontrol grubunda mortalite oranı %3.6 artmış olarak bulunmuştur.

Finfer S, etal. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009.

4)Kanıtların eksikliği!!

Temel olarak glukoz monitörizasyonundaki ve tedavi teknolojilerindeki sınırlılık neden olabilir.

Daha iyi teknolojik monitörizasyon ve insulinin kontrollü verimini sağlayan teknolojik gelişmeler hipoglisemik epizotların olmasını engelleyerek daha yumuşak bir glisemik kontrol sağlayabilir

6) Diyabetli hastalarda GK?

*Sıkı glisemik kontrol DM li hastlarda DM'siz hastalara göre daha az etkilidir.

Rady MY, et al. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. Mayo Clin Proc 2005

Egi M, Bellomo R, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med 2008

*DM'lu hastalar hiperglisemiden DM olmayan hastalardan daha az etkilenirler. Hiperglisemiye karşı kronik adaptasyonları vardır.

Bu nedenle DM'lu hastalarda bir eşik değer söylemek güçtür.

*Ayrıca Tip1 ve Tip 2 DM tedavisi ayrı olduğundan bunlarda uzun etkili insulinler kullanılmalıdır ve glisemik kontrol çalışmalarında yer bulmamıştır.

Puskas F, et al. Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg 2007

Krinsley JS. Blood glucose control in critically ill patients: the impact of diabetes. Crit Care Med 2009

Glukoz monitörizasyonu?

- Kapiller, merkez laboratuvar, kan gazı?
- Hipoperfüzyon, hipotermi, anemi özellikle kapiller KŞ bakılırken yanıltıcıdır.
- Laboratuvar daha güvenlidir.
- Plazma glukoz konsantrasyonu tam kandan %11 fazladır. Ciddi anemisi olanlarda plazma volümü daha fazla olduğu için kan şekeri seviyesi daha yüksek bulunur.
- L-dopa, dopamin, mannitol, asetaminofen, ind. bilirubinin çok yüksek olması, şiddetli hiperlipidemi, ürik asitin artması, maltoz (Ig solüsyon-larında), periton diyaliz solüsyonları….KŞ ölçümünde karışıklığa neden olabilirler.
- Bu değişkenlikler olması gerekenden az veya çok insulin dozu uygulanmasına neden olur.

İnsülin Protokolleri

- YBU'lerinde KŞ bakılması hasta başına 3.5-9 dk almaktadır.

(iş gücü/zaman)…saat başı, iki saatte bir…

Wilson M, et al. Intensive insulin therapy in critical care: a review of 12 protocols. Diabetes Care 2007

*Subkutan insulin perioperatif dönem kritik hastada önerilmez. Çünkü deri perfüzyonu ve dolayısıyla emilim değişkendir.

*Ayrıca sc insulinler hızlı etkili analoglar olsa bile yavaş ve uzun etkilidirler. Bu süre zarfında yavaş salınım tehlikeli olabilir (hipoglisemi!!)

* IV insülin (enjeksiyon ve bolus kombinasyonu)

Perioperative management of blood glucose in adults with diabetes mellitus

Authors
Nadia A Khan, MD, MSc
William A Ghali, MD, MPH
Enrico Cagliero, MD

Section Editors
David M Nathan, MD
Stephanie B Jones, MD

Deputy Editor
Jean E Mulder, MD

Glycemic targets — Beyond avoidance of marked hyperglycemia and hypoglycemia, the optimal perioperative glucose targets are unclear. Although there are varying opinions on what the target blood glucose should be, in our practice, we aim to keep glucose readings between 140 and 200 mg/dL (7.8 to 11 mmol/L). In a meta-analysis of 12 randomized trials (1403 patients with diabetes) comparing intensive (<120 or <150 mg/dL [<6.7 or <8.3 mmol/L]) versus conventional (variable) glycemic control in the perioperative period, intensive glycemic control perioperatively was not associated with any reductions in infectious complications, cardiovascular events, or mortality, but was associated with increased risk of hypoglycemia [28]. Among the trials, the mean difference in achieved blood glucose levels between the intensive and conventional groups ranged from -13 to -91 mg/dL (0.72 to 5.0 mmol/L).

Diabetes guideline bodies recommend glycemic targets of between 110 and 180 mg/dL (6.1 to 10 mmol/L) for non-critically ill hospitalized patients [29,30]. However, a less stringent glucose target (200 mg/dL [11 mmol/L]) may be considered depending on risk for hypoglycemia and also potentially in the general patient population (given the acknowledged lack of evidence to support more stringent targets). The risk of hypoglycemia can be reduced by frequent glucose monitoring and carefully designed management protocols. The American Diabetes Association (ADA) has endorsed fasting glucose goals of <140 mg/dL (7.8 mmol/L) for general hospitalized patients, with random glucose readings <180 mg/dL (10 mmol/L) [31,32]. (See "Management of diabetes mellitus in hospitalized patients", section on 'Glycemic targets' and "Glycemic control and intensive insulin therapy in critical illness".)

Perioperative glycaemic control for diabetic patients undergoing surgery (Review)

Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D

THE COCHRANE COLLABORATION®

Perioperative management of blood glucose in adults with diabetes mellitus

Authors
Nadia A Khan, MD, MSc
William A Ghali, MD, MPH
Enrico Cagliero, MD

Section Editors
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Glycemic control and intensive insulin therapy in critical illness

Authors
Renee D Stapleton, MD, PhD
Daren K Heyland, MD, FRCPC, MSc

Section Editors
Polly E Parsons, MD
Adrienne G Randolph, MD, MSc

Deputy Editor
Geraldine Finlay, MD

Summary — In mixed adult populations of critically ill medical and surgical patients, IIT (target blood glucose of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) increased the incidence of severe hypoglycemia and either increased mortality or had no effect on mortality, when compared to the more permissive blood glucose ranges of 140 to 180 mg/dL (7.8 to 10 mmol/L) and 180 to 200 mg/dL (10 to 11.1 mmol/L). Similar trends have been noted in children.

SUMMARY AND RECOMMENDATIONS

Hyperglycemia is associated with poor clinical outcomes in critically ill children and adults. (See 'Effects of hyperglycemia' above.)

While most clinicians agree that such glycemic control is a desirable intervention, the optimal blood glucose range is **controversial**. (See 'Glycemic control' above.)

For hyperglycemic critically ill adult patients:

- We recommend a blood glucose target of 140 to 180 mg/dL (7.7 to 10 mmol/L), rather than a more stringent target (eg, 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) (**Grade 1A**). (See 'General approach' above.)
- We also suggest a blood glucose target of 140 to 180 mg/dL (7.7 to 10 mmol/L), rather than a more liberal target (eg, 180 to 200 mg/dL [10 to 11.1 mmol/L]) (**Grade 2C**). (See 'General approach' above.)
- To achieve our target blood glucose, we minimize our use of intravenous fluids that contain glucose and administer insulin only when necessary. A widely accepted insulin regimen has not been established but short-acting insulin is preferred. Careful monitoring of blood glucose is necessary to achieve glycemic control while avoiding the potential harmful effects of hypoglycemia. (See 'General approach' above and 'Hypoglycemia' above.)

GENERAL APPROACH — We recommend a blood glucose target of 140 to 180 mg/dL (7.7 to 10 mmol/L) in most critically ill adult patients, rather than a more stringent target (eg, 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) or a more liberal target (eg, 180 to 200 mg/dL [10 to 11.1 mmol/L]). This range avoids marked hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target. The following evidence supports our approach:

- Hyperglycemia, defined as a blood glucose level greater than 180 to 200 mg/dL (10 to 11.1 mmol/L), is associated with poor clinical outcomes. (See 'Effects of hyperglycemia' above.)
- Intensive insulin therapy (IIT, target blood glucose range of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) significantly increases the incidence of severe hypoglycemia. Its effect on mortality is uncertain, since various randomized trials have reported increased mortality, no effect on mortality, or decreased mortality. (See 'Glycemic control' above and 'Hypoglycemia' above.)
- Patients managed with our blood glucose target had a significantly lower mortality and incidence of hypoglycemia in the largest trial that directly compared our recommended blood glucose target to IIT. (See 'NICE-SUGAR trial' above.)

Rehberler?

Recommendations for Glycemic Control in the Perioperative Period

Location	American College of Endocrinology[171]	Canadian Diabetes Association[172]	American Diabetes Association[171]	American Heart Association/ American College of Cardiology[a173]	Society of Thoracic Surgeons (for cardiac surgery)[174]
Intensive care unit	Between 140 and 180 mg/dL; generally <180 mg/dL	<110mg/dL	Between 140 and 180 mg/dL; generally <180 mg/dL	110–180 mg/dL	Generally; <180 mg/dL ventilator dependent in ICU >3 d; <150 mg/dL
Intraoperative	<150 mg/dL	90–180 mg/dL	<150 mg/dL		<180 mg/dL
Perioperative	<140 mg/dL premeal or <180 mg/dL (random)	90–180 mg/dL	<140 mg/dL premeal or <180 mg/dL (random)	NA	<180 mg/dL

NA= not addressed specifically; ICU = intensive care unit.

[a] Guidelines were based on earlier studies and older recommendations from the American College of Endocrinology and the American Diabetes Association.

SONUÇ

- Sıkı glisemik kontrolün (<110mg/dl) etkinliği ispatlanmamıştır.

- Hipoglisemi riskini 3-6 kat artırmaktadır.

SONUÇ

- Hiperglisemi ciddiye alınmalı, gözden kaçırılmamalı
- 140-180 mg/dl
- Hipoglisemiye neden olunmamalı

TEŞEKKÜRLER