From “inconvenient truth” to “assault on reason”

To the Editor:

Strict glycemic control (SGC) carries the risk of severe hypoglycemia (SH). Indeed, with SGC the incidence of SH (defined as a blood glucose concentration <40 mg/dL) is five- to ten-fold higher as compared with a conventional blood glucose strategy (1, 2).

To determine the risk factors for SH and define its outcomes, Drs. Krinsley and Grover (3) performed a retrospective database review, including a case-control analysis that matched each patient with SH with three controls. Cases and controls were extracted from a series of patients during three consecutive periods, during which no standardized approach to glycemic monitoring or management was present, a program of SGC was instituted (targeting 80–140 mg/dL), and a more strict SGC was applied (targeting 80–125 mg/dL), respectively. The main finding was that mortality was 56% among the 102 patients with SH vs. 40% among controls. Diabetes, septic shock, renal insufficiency, mechanical ventilation, severity of illness, and treatment in the SGC period were identified as independent risk factors for SH. Multivariable logistic regression analysis identified SH as an independent predictor of mortality for the entire cohort (odds ratio [OR], 2.28; 95% confidence interval [CI], 1.41–3.70). From these results, the investigators suggest “safer implementation of SGC will accrue following development of new technologies to monitor glycemic levels, perhaps on a continuous basis.” Does this mean that, in other words, at present SGC is an “unsafe” strategy?

Are we to understand that approximately 30% of patients with SH were not on insulin therapy in the preceding 12 hrs? Also, very much in contrast to the studies by van den Berghe (1, 2), was only a minority of patients on intravenous insulin therapy? If so, this study hardly offers an answer to the question whether SH with SGC truly influences morbidity and mortality.

Dr. Suh and colleagues (4) recently showed that hypoglycemia-induced oxidative stress and neuronal death are attributable primarily to the activation of neuronal NADPH oxidase during glucose reperfusion. Of note, the degree of oxidative stress and neuronal death increased with increasing glucose concentrations during the reperfusion period. These results suggest that not SH by itself, but high blood glucose concentration following hypoglycemic coma, can initiate neuronal death. The study by Drs. Krinsley and Grover (3) is retrospective in its design, and it may not be possible to retrieve data on how severe hypoglycemia was corrected for each individual case. The authors, however, may provide us with their protocol for correction of severe hypoglycemia.

From “inconvenient truth” to an “assault on reason”: Over the last years we have “inconveniently” learned that accepting high blood glucose concentrations, intrinsic to severe illness, is harming our patients. However, the medical literature is loaded, and dominated, with reports and opinion pieces arguing against SGC, at least in part based on the finding that SGC comes with an increased risk for SH. Let us be careful in interpreting data with regard to SGC. Indeed, we consider the risk of SH to not be a reason for failing to implement SGC.

Marcus J. Schultz, MD, PhD, Mart J. de Graaff, University of Amsterdam, Amsterdam, The Netherlands; Michael A. Kuiper, Medical Center Leeuwarden, Leeuwarden, The Netherlands; Peter E. Spronk, Gelre Hospital, Lukas–Apeldoorn, The Netherlands

REFERENCES


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The authors reply:

We concur heartily with the conclusions of Drs. Schultz, de Graaff, Kuiper, and Spronk that “we consider the risk of SH [severe hypoglycemia] to not be a reason for failing to implement” tight glycemic control. In fact, the sensitivity analysis included in our manuscript makes the point that the beneficial effect of tight glycemic control would not have been eliminated unless the rate of SH quadrupled and the mortality attributable to an episode doubled. Recognition of the potential for harm should foster efforts for safer implementation of insulin treatment protocols, not abandonment of the therapy.

The data of Dr. Suh and colleagues are indeed very intriguing (1). The effect of glycemic variability, known in diabetics to increase oxidative stress (2), is a topic that we are currently investigating.

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REFERENCES


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Not euthanasia, simply compassionate clinical care

To the Editor:

Dr. Kompanje and colleagues (1) describe a case of “Euthanasia in Intensive Care” that involved a competent patient with a devastating neurologic condition who chose to refuse continuation of life support and to be allowed to die. The salient ethical principles in this case are: a) the right of competent patients to refuse any and all unwanted medical treatments; and b) the obligation of clinicians to assure that patients are comfortable and without suffering through the dying process. These principles are ethically and legally accepted in North America and, I believe, most of Western Europe. This case conformed to both of these principles. Describing this as a case of euthanasia is unnecessarily provoca-
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Euthanasia in the critical care setting

To the Editor:

The recent article by Dr. Kompanje and colleagues (1), describing the “intentional termination of life” of an ICU patient with locked-in syndrome, raises important clinical, ethical, and legal questions.

Despite its phenomenal progress, modern medicine has created many new problems. We are now faced with dramatically explicit questions: Does the patient have the right to be killed? Is it the doctor’s duty to grant such a request? In general, does the doctor have the right to deliberately end a patient’s life?

I would like to propose two considerations. Firstly, we must avoid a fundamental misunderstanding: that what is established by law is per se ethically acceptable. Clearly, each country has sovereignty over its own legislation, but the legal and ethical planes are distinct, even if both contribute to every decision-making process. (The legal plane defines what, in a given society and period, is recognized as lawful; the ethical plane essentially concerns the intrinsic value of an action, its “goodness” and acceptability.) Similarly, merely observing that a practice exists does not make it ethically acceptable. On such crucial matters, I feel it is essential that “unless ethics becomes a merely reactive and adaptive mechanism to a changing reality, ethical and legal norms—what ought to be done—should not be deduced from observed behaviors—what is done. Instead, they need to be elaborated from moral principles and values” (2).

Secondly, while we have progressed from the medical paternalism of the past, the respect which is rightly accorded to the principle of autonomy (3) must not be allowed to box the doctor into a sort of moral neutrality. The doctor is not an ethnically “neutral” subject, a blank sheet on which patients may express whatever wish they may have. Doctors also have ethical convictions, and the doctor–patient relationship therefore represents the meeting of two autonomies. From the confrontation, and full and frank exchange, between these two subjects (the “therapeutic covenant”) must arise a shared decision that also considers the ethical dimension. In the case of conflict on the ethical plane, I believe the doctor should have the right of conscientious objection.

The dramatic condition of the patient described by Dr. Kompanje and colleagues (1) brings us face to face with the objective limits of medicine. However, I personally continue to believe that there is a substantial difference between killing and allowing to die (4), and I agree with the recommendations made on this for the intensive care setting (5). We have the duty to look after our patients and to palliate suffering, even at the price of suppressing—if necessary—the patient’s consciousness.

In intensive care also, the key issues in evaluating the ethical acceptability of physicians’ choices and actions are intention and means employed. On the ethical plane, the intention to alleviate suffering is quite different from the voluntary and deliberate action of taking a person’s life.

In my opinion, the universal imperative “not to kill” is still valid, and I sincerely hope that euthanasia does not become an accepted option for intensive care patients.

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REFERENCES


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A barbiturate was the only or the most potent ant (pancuronium) (2). Another Dutch study of thiopental was followed by a muscle relaxant, remaining 45 cases (80.4%), the administration of thiopental with a muscle relaxant was chosen. The administration died immediately following the administration of thiopental. In a Dutch study, the administration of the pancuronium bromide, already available at the bedside, was unnecessary. The assumption of Dr. Truog that the patient was ventilator dependent is probably the main reason why he thinks this is not a case of euthanasia given that, in his opinion, withdrawal of the ventilator was certain to lead to death, regardless of whether any medications were administered. However, the suggestion of Dr. Truog that the administration of 30 mg midazolam and 1.4 g thiopental could not have led to death following ventilator withdrawal is in contradiction to the publications discussed above and the course of our patient. We therefore have described the case as an intended and deliberate termination of life (euthanasia) in the intensive care unit. The clinical situation of the patient and the actions taken in combination with the medications used are not consistent with normal palliative care in the Netherlands, but only with the process of euthanasia. We did not intend to be provocative in this way. True, euthanasia by the method described is very rare in intensive care in the Netherlands. Withdrawal of treatment, followed by the administration of palliative (not lethal) doses of opioids and/or benzodiazepines such as midazolam or propofol, is very common. In the Netherlands, thiopental has no place in normal palliative care because it can cause the immediate death of the patient. We also agree with Dr. Giannini that the patient was ventilator dependent is probably the main reason why he thinks this is not a case of euthanasia given that, in his opinion, withdrawal of the ventilator was certain to lead to death, regardless of whether any medications were administered. However, the suggestion of Dr. Truog that the administration of 30 mg midazolam and 1.4 g thiopental could not have led to death following ventilator withdrawal is in contradiction to the publications discussed above and the course of our patient. We therefore have described the case as an intended and deliberate termination of life (euthanasia) in the intensive care unit. The clinical situation of the patient and the actions taken in combination with the medications used are not consistent with normal palliative care in the Netherlands, but only with the process of euthanasia. We did not intend to be provocative in this way. True, euthanasia by the method described is very rare in intensive care in the Netherlands. Withdrawal of treatment, followed by the administration of palliative (not lethal) doses of opioids and/or benzodiazepines such as midazolam or propofol, is very common. In the Netherlands, thiopental has no place in normal palliative care because it can cause the immediate death of the patient. We also would like to thank Dr. Gianini for his comments on our article. We share his view that modern medicine has created many new problems and confronts physicians with very difficult questions. We also agree that the plane of ethics and the plane of the law differ. We are, however, convinced that euthanasia is justified in the ethical plane given certain very strict safeguards and conditions. Given these ethical safeguards, euthanasia is legally allowed in the Netherlands. We have had a very long, thorough, and complex debate on the ethical justification of euthanasia in the Netherlands among physicians, philosophers, jurists, and the general public. We agree with Dr. Giannini that the physician is not an instrument obligated to carry out patients' wishes; in the Netherlands, a physician is not obliged to perform euthanasia. On the other hand, a moral responsibility to end the suffering of a patient at his request can motivate the physician to perform euthanasia. In some cases, this can be accomplished by withdrawing treatment. However, when this is not likely to result in the death of a patient, alleviation of suffering can be the sole reason and only justification to end a person's life. As we have argued, this is a very rare occurrence in the clinical practice of intensive care.
Severe hypoglycemia in critically ill: Risk and outcomes

To the Editor:

We want to congratulate Drs. Krinsley and Grover (1) for their efforts to define risk factors for hypoglycemia in the intensive care unit and to determine its effects on outcome, as published recently in Critical Care Medicine. As they note, we published in this journal on the same topic (2, 3). When accounting for time spent in the intensive care unit, Acute Physiology and Chronic Health Evaluation (APACHE) score at admission, age, and sex, we found no association between hypoglycemia and mortality, in contrast to Drs. Krinsley and Grover.

In their article, Drs. Krinsley and Grover express their concern about methodologic aspects of our study. Like them, we used a nested case-control design. This is an efficient design combining the advantages of follow-up studies (well-defined cohort, absolute risk estimation) with those of a case-control study (high efficiency and power), with additional close matching on time that allows calculation of incidence rate ratios. This close matching on time also reduces major confounding by severity of disease, which may not have been adjusted for completely by the matching and multivariate regression analysis. Inclusion of these two different types of events therefore introduces risk factors for hypoglycemia as an independent risk factor for death. Hence, it is possible that hypoglycemia induced by intensive insulin therapy may have reduced a portion of the potential benefit (1) (emphasis added).

The respondents state that the “main weakness of both our studies is the number of hypoglycemic episodes.” A fortunate thing, indeed! Because the effect of severe hypoglycemia cannot be assessed in a randomized controlled intervention trial, case control and multivariate logistic regression analyses remain our most powerful tools. We are very enthusiastic about the idea of creating an international registry of hypoglycemic events and patients. Let’s agree on standardized data points and analytic methods and we would be pleased to collaborate with our friends from the Netherlands on this project. Perhaps we could ask for support from the society for this important clinical project.

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The authors reply:

We read with great interest the comments of Drs. Vriesendorp, DeVries, Rosendaal, and Hoekstra and appreciate their insights into the methodologic differences that may underpin the different conclusions we reached regarding the deleterious effect of severe hypoglycemia. We would like to point out that the investigators of the Leuven II study reached a conclusion similar to ours: “... logistic regression analysis identified hypoglycemia as an independent risk factor for death. Hence, it is possible that hypoglycemia induced by intensive insulin therapy may have reduced a portion of the potential benefit” (1) (emphasis added).

The respondents state that the “main weakness of both our studies is the number of hypoglycemic episodes.” A fortunate thing, indeed! Because the effect of severe hypoglycemia cannot be assessed in a randomized controlled intervention trial, case control and multivariate logistic regression analyses remain our most powerful tools. We are very enthusiastic about the idea of creating an international registry of hypoglycemic events and patients. Let’s agree on standardized data points and analytic methods and we would be pleased to collaborate with our friends from the Netherlands on this project. Perhaps we could ask for support from the society for this important clinical project.

James S. Krinsley MD, FCCM, Aarti Grover, MD, Stamford Hospital, Stamford, CT
Tight glucose control and hypoglycemia

To the Editor:

We read with interest the article by Drs. Krinsley and Grover (1), and the accompanying editorial by Nasraway (2), both published in the October issue of Critical Care Medicine. However, we feel concerned by the conclusions drawn by the authors; i.e., that tight glucose control by intensive insulin treatment may improve outcome, while the data shown a) highlight an increased rate of hypoglycemia; and b) clearly identify hypoglycemia as an independent risk factor of mortality by the case-control approach and by multivariate logistic regression analysis. Based on data from a before-and-after observational study, Drs. Krinsley and Grover conclude that tight glucose control targeted to achieve intermediate normal or near-normal levels of blood glucose may improve mortality and morbidity in critically ill patients. However, they provided only rather limited data regarding patient characteristics and clinical conditions. Importantly, other modifications in the therapeutic management might have influenced outcome. In our view, these findings warrant further research a) to prevent hypoglycemia during tight glucose control, namely by a careful training of the nursing teams; b) to define the target range of blood glucose associated with the best risk-to-benefit ratio; and c) to characterize more accurately patients in whom tight glucose control is associated with improved outcome. Another option may be to abandon tight glucose control until these pending issues are resolved, as recently suggested (3).

Finally, reading the editorial of Dr. Nasraway (2), stating that the results of two prospective randomized controlled and multicentric trials (the German Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP] and the European Glucontrol studies) (4, 5) “were fatally undermined by protocol violations, experimental design flaws, and insufficient sample size” (2), we are deeply concerned that the principles of evidence-based medicine are not only fully acknowledged but rather neglected.

Both are carefully prepared clinical trials, fulfilling the “gold standard” of research in clinical medicine and will be published soon. Because only preliminary results of these trials have been presented in international meetings, such comments before the publication of the final data are not in accordance with good scientific practice and should be omitted. Indeed, the data submitted for publication obviously will undergo a careful peer-review process, implying a fair interpretation and a formal acknowledgment of the limitations. The importance and relevance of such multicenter large trials is much larger than studies performed in one center and than hypothesis-generating retrospective studies, which are of minor value in clinical decision-making. This is what we should do for the sake of our patients in the intensive care unit.

Jean-Charles Preiser, MD, PhD, Frank Brunkhorst, University Hospital Centre of Liege, Liege, Belgium (JCP); Friedrich-Schiller-University Jena, Jena, Germany (FB)

REFERENCES


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The authors reply:

We appreciate the comments of Drs. Preiser and Brunkhorst about our article (1) and agree completely that training of clinical staff to prevent severe hypoglycemia and further definition of most appropriate glycemic goals for different patient populations are worthy goals. However, we do not believe that the option of abandoning tight glucose control “until these pending issues are resolved,” akin to “throwing out the baby with the bath water,” is appropriate.

The respondents mention that the manuscript provided only “rather limited data regarding patient characteristics and clinical conditions.” We refer readers to reference 12 in the article (2). This observational cohort, comprising the 5,365 patients in the current hypoglycemia study, represents a large expansion of our center’s initial interventional trial, published in 2004 (3). There were 2,666 patients treated before the institution of tight glucose control and 2,699 afterward. Multivariate analysis demonstrated improvement in mortality associated with the tight glucose control era in the medical and surgical, but not trauma, subpopulations, as well as in the cohort as a whole.

Could these findings have been due to a “Hawthorne effect”? Our intensive care unit practices evidence-based recommendations and guidelines, such as “ventilator bundles,” low tidal volume ventilation in acute lung injury, and the use of drotrecogin-alpha in selected patients with septic shock and very high acuity of illness; moreover, routine aspects of care in the intensive care unit are very largely protocol driven. Nevertheless, the potential confounding effect of the application of these interventions has been, we believe, dwarfed by the implementation of tight glucose control (starting on February 1, 2003). In support of this, we report here the yearly hospital mortality rate of patients admitted to the intensive care unit from 2000 through 2007: 20.6%, 20.1%, 20.6%, 14.9%, 15.5%, 14.2%, 15.5%, 15.2%, 13.9%, and 14.4%. These numbers do not reflect incremental improvements in the delivery of care to this critically ill group of patients; instead, we believe that the abrupt, dramatic, and persistent decrease in mortality is due to intensive glycemic management.

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Acid base balances

To the Editor:

I read with interest the concise definitive review “Disorders of acid base balance” in the November 2007 issue of Critical Care Medicine (1). In the review, Dr. Kellum points out correctly that large volumes of saline cause a hyperchloremic metabolic acidosis, given that the chloride concentration increases proportionately more than sodium because its initial concentration in serum is lower. However, the following thought experiments give additional insights.

Assume that the weight of a person = 50 kg; body water is 50 × 0.6 = 30 L. Serum Na = 140 mmol/L and serum chloride = 100 mmol/L. Strong ion difference (SID) before addition of any normal saline = 40 mmol/L. The potassium, calcium, and magnesium are ignored just to keep the calculations simple. The expected rise in serum sodium (and chloride) is calculated based on the total body water (2):

Scenario 1: Infusion of 10 L of Normal Saline. Total Na is 140 × 30 = 4200 mmol. Total chloride is 100 × 30 = 3000 mmol. Adding 10 L of normal saline (1540 mmol of Na and 1540 mmol of Cl) yields:

Body sodium becomes 4200 + 1540 = 5740 mmol. Body chloride becomes 3000 + 1540 = 4540 mmol. Body water goes up by 10 L to 30 + 10 = 40 L. Final concentration of Na is 5740/40 = 143.5 mmol/L. Final concentration of Cl is 4540/40 = 113.5 mmol/L.

The new SID is 143.5 − 113.5 = 30 mmol/L.

Scenario 2: Addition of “Pure Sodium Chloride.” Consider adding the same amount of sodium chloride as above without fluids:

Body sodium becomes 4200 + 1540 = 5740 mmol. Body chloride becomes 3000 + 1540 = 4540 mmol. Body water remains the same at 30 L. Final concentration of Na is 5740/30 = 191.3 mmol/L. Final concentration of Cl is 4540/30 = 151.3 mmol/L.

The new SID is 191.3 − 151.3 = 40 mmol/L. The SID is the same as before; it has not changed!

Scenario 3: Addition of “Pure Water” (Dilution). Body sodium remains the same at 4200 mmol. Body chloride remains the same at 3000 mmol. Body water increases to 30 + 10 = 40 L. Final concentration of Na is 4200/40 = 105 mmol/L. Final concentration of Cl is 3000/40 = 75 mmol/L.

The new SID is 105 − 75 = 30 mmol/L. The SID has changed to the same extent as in the first scenario when 10 L of normal saline was added.

The reverse can be shown if 10 L of free water is removed (concentration)!

The crucial insight is that it is the water content of the infused sodium chloride solution that makes the difference to SID. In fact, for the same amount of NaCl, it can be shown that a 3% solution will change SID less than a 0.9% solution. It is thus dilutional acidosis and contraction alkalosis with a fresh insight!

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The authors reply:

Dr. George John is completely correct. The strong ion difference of the infusate and volume infused determine the effect on the patient’s strong ion difference and therefore pH. He correctly points out that hypertonic (3%) saline actually has less effect on pH compared with isotonic (0.9%) saline, even though the chloride concentration is higher—although this is only true provided that a smaller volume of the 3% solution is administered.

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