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Randomized Control Trials

TICACOS international: A multi-center, randomized, prospective controlled study comparing tight calorie control versus Liberal calorie administration study

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SUMMARY

Since the first TICACOS study, 3 additional studies have been published comparing a medical nutrition therapy guided by indirect calorimetry to a regimen prescribed on the basis of predictive equations. A recent guidelines document included a meta-analysis including these 4 papers and found a trend for improvement (OR 0.98–1.48) in favor of medical nutrition therapy guided by indirect calorimetry in terms of survival. The aim of our study was to perform a multicenter prospective, randomized, controlled non blinded study in critically patients to assess the added value for measuring daily resting energy expenditure as a guide for nutritional support. The primary objective was to decrease infectious rate of these critically ill patients.

Material and methods: This phase III, multi-center, randomized, controlled non blinded study was planned to include 580 newly-admitted, adult ventilated ICU patients that were planned to stay more than 48 h in the ICU departments. The nutritional support was aimed to meet 80–100% of energy requirement measured by indirect calorimetry. The calorie needs were determined by IC in the Study group and by an equation (20-25 kcal/kg ideal body weight/day) in the Control Group. The ICU staff was trained to strive to supply 80–100% of a patient's energy requirements through artificial nutrition, preferably enteral feeding. Primary endpoint was infection rate and secondary endpoints included other morbidities and mortality during ICU, at 90 and 180 days. Comparison between the study and the control group was performed using T test for equality of means (independent samples test). Correlations were performed using the Pearson correlation test. A p level of 0.05 or below was considered as significant. Cross tabs procedure used Chi-square test for testing differences in complication rates, length of stay and length of ventilation. Correlations between energy balances and complications was also be tested using one way analysis as well as ANOVA analysis between groups and within groups. Kaplan Meir curves assessed the proportion of surviving patients in the 2 groups.

Results: Seven centers with a calorimeter available participated to the study. Due to slow inclusion rate, the study was stopped after 6 years and after inclusion of 417 patients only. From the 417 intended to treat patients, 339 followed the protocol. There was no differences between control and study groups in terms of age, sex BMI, SOFA (7.1 ± 3.1 vs 7.4 ± 3.3) and APACHE II scores (22.4 ± 7.9 vs 22.2 ± 7.4). The rate of infection (40 vs 31), including pneumonia rate, need for surgery, dialysis requirement, length of ventilation, ICU length of stay, and hospital length of stay were not different between groups. Mortality (30 in the control vs 21 in the study group) was not significantly different between groups. The decreased

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mortality observed in the study group when added to previous studies may have a positive effect on the meta-analysis previously published.
Conclusion: Tight Calorie Control guided by indirect calorimetry decreased the rate of infection and mortality but not significantly. This may be explained by the not relatively small sample size. There results together with the previous 4 prospective randomized studies, may improve the results of the meta-analysis exploring the effects of IC guided nutrition on mortality.

1. Introduction

Since the first TICACOS pilot study [1] that showed a trend for improved survival in per protocol patients receiving energy according to indirect calorimetry target, 3 additional studies have been published comparing a medical nutrition therapy guided by indirect calorimetry to a regimen prescribed on the basis of predictive equations. The SPN study [2] has found an improvement in the rate of infection acquired in the hospital and a decrease in length of ventilation. Petros et al. [3] have confirmed the decrease in nosocomial infection, but the EAT-ICU study [4] failed to confirm these findings. A recent guidelines document [5] included a meta-analysis including these 4 papers and found a trend for improvement (OR 0.98–1.48) in favor of medical nutrition therapy guided by indirect calorimetry. The ASPEN [6] and the recent ESPEN [5] guidelines recommend to use IC if available and recognize the serious limitations related to the use of predictive equations that could lead to a high level of inaccuracy [7]. Inspired by the limitations of the previous TICACOS pilot study, we conducted a multicenter prospective randomized study trying to administer tight calorie control while ensuring increased daily protein intake, while avoiding non nutritional calories intake. The aim of our study was to perform a prospective, randomized, controlled non blinded study in critically ill patients to assess the advantages for measuring daily resting energy expenditure as a guide for nutritional support. The primary objective was to decrease rate of infections of these critically ill patients.

2. Methods

2.1. Subjects

This phase III, multi-center, randomized, controlled non blinded study was planned to include 580 newly-admitted, adult ventilated ICU patients that were planned to stay more than 48 h in the department. The study was approved by all 7 institutional review boards (IRB) and prior to randomization, informed consent was obtained from the patient, his/her family or legal representative or an independent physician according to the local IRB decision. All the patients over 18 years old, ventilated and supposed to stay more than 48 h, were eligible for the study. If FIO2 was higher than 60%, if there was a need for inhaled nitric oxide therapy, continuous renal replacement therapy, if there was an evidence of air leak like through chest drains, or in case of pregnancy, the patients were excluded, as well as if they were included in another study. Patients admitted for complications after head trauma or open heart surgery were also excluded due to expected longer length of stay.

In the study group the nutritional support was aimed to meet 80–100% of energy requirements targeted by indirect calorimetry measurements. Indirect calorimetry was performed using the device available in each center: Deltatrac II (Datex-GE, Finland) in n centers and COVX (GE, USA) as well as Quark (Cosmed, Italy) in others. Calibration and methods were performed as described [8] respecting the rules of procedure described by our group [9]. Enteral Nutrition (EN) was preferred but Parenteral Nutrition (PN) was added if EN caloric supply< 90% calculated needs, The calorie needs were determined by IC in the study group and by an equation (20-25 kcal/kg ideal body weight/day) in the control Group. Indirect calorimetry was performed in the control group as well, but calories were supplied according to 20–25 kcal/kg/day equation. In the control group, this target was obtained using the local protocol.

The primary objective was the rate of new infections according to HELICS classification [10] (See appendix 1). The secondary endpoints included metabolic control: success of tight caloric control (daily, accumulative and maximum negative energy balance), glucose concentration, insulin administration, rate of hypoglycemic events,. Other endpoints included improvement in organ functions evaluated by daily SOFA score, the rate of non-infectious complications: requirement for surgery, the length of ICU stay and of assisted ventilation (LOS and LOV), the rate of discharge to rehabilitation and mortality in the ICU, in the hospital and at 90–180 days.

Patients eligible were randomly assigned by a concealed, computer-generated program to 2 groups, the study and the control group, within 48 h of ICU admission. The administration of caloric requirements was performed as followed. Patient' caloric requirements were defined as: for the study group, the repeated measured resting energy expenditure (REE) obtained by IC in kcalories/day and for the control group as 25 kcal/kg body weight/day. Weight was obtained by weighing beds if available (Hillrom, USA) or by history or information obtained from the family. The ICU staff was trained to strive to supply 80–100% of a patient's energy requirements through artificial nutrition, preferably utilizing EN. PN was added if EN caloric supply <90% caloric requirements from day 3 onwards. Nutrition formulas used preferentially products enriched protein to reach a protein intake. Enteral formulas included protein enriched formulas like Promote (Abbott, USA) or Peptamen A/F (Nestle, Switzerland) mainly. Parenteral nutrition was administered using an protein enriched solution: Triomel N9 (Baxter, USA). The complete composition of these products is available in Appendix 2.

In patients with a functional gastrointestinal tract, enteral feeding via a nasogastic tube was started at 20 ml/h and increased progressively every 4 h to reach daily caloric requirements. A nutritional formula was prescribed according to the unit policy with a preference for polymeric formulas. The nutritional formula was delivered continuously as long as the patient tolerated. The gastric residual volume was measured every 4–6 h and the mode of feeding was modified, if gastric residual volume >500 mL or, if there was occurrence of vomiting, diarrhea more than 3 times/day. In such a case, the enteral feeding was be stopped and replaced by parenteral nutrition. If gastric residual volume was between 150 and 500 mL, the enteral feeding rate was reduced and/or prokinetic therapy (metoclopramine 10 mg x 3/day or erythromycin 150 mg x 3/day) was initiated. The regimen was maintained if the residual volume remained below 500 ml and >90% of caloric needs was met by EN alone,. Parenteral nutrition was initiated, either alone or as supplemental nutritional support, if a contraindication for EN was

present on admission, a contraindication for EN occurred during the trial, if gastric residual volume >500 mL, or if EN delivered (or is expected to deliver) ≤ 90% daily caloric requirements. Supplemental non nutritional calories such as dextrose 5% or propofol were noted and added to the total energy intake. Continuous insulin therapy was administered to maintain blood glucose levels between 100 and 180 mg/dL.

Anthropometric parameters including age, sex, weight, height, body mass index (BMI), admission day APACHE II and daily SOFA scores were collected. Main and secondary diagnosis were noted. We tracked electrolytes, glucose, BUN, creatinine, liver function tests, blood count, total protein and albumin, prealbumin. Resting energy expenditure was reported at each measurement. In addition to REE, oxygen consumption (in mL/min) (VO2), carbon dioxide production (in mL/min) (VCO2) and the respiratory quotient (RQ) were collected. Predictive equations were also calculated using Harris Benedict equations. These equations were used if indirect calorimetry was not possible to be performed due to contraindications. Daily calories and protein were followed and noted according to the route administration (PN or EN). Daily and total calorie balance was obtained using a computerized information system (iMD*soft,* Ramat Gan, Israel) or manual chart. The complications reported included new infections (see appendix 1) including catheter related sepsis, pneumonia, urinary tract infection, abdominal or soft tissue infections. Surgical requirement, new pressure sore, poor wound healing, requirement of packed cells transfusion, renal replacement therapy, liver dysfunction or polyneuropathy were also noted. Approval was obtained from each patient or his/her next of kind. In countries where it was applicable, a neutral physician gavehis approval until the patient or his legal representative could express themselves. All the centers obtained agreement from the local IRBs. The study was registered in ClinicalTrials number 4329.

2.2. Statistical analysis

2.2.1. Sample size

The proposed number of patients in order to reach a statistically significant difference between the two groups was 280 in each group or a total of 560 patients. This number was based on the working hypothesis of achieving a 66% decrease in infection rate (Minimal risk ratio of 3), based on the Rubinson study [8] that demonstrated that improved energy balance decreased bacteremia by 75%. With a power of 80%, significant difference was calculated to be reached with 560 patients. Interim analysis was performed after the inclusion of 280 patients. Results were expressed in mean ± standard deviation. Comparison between the study and the control group was performed using T test for equality of means (independent samples test). Correlations were be performed using the Pearson correlation test. A p level of 0.05 or below wasl considered as significant. Cross tabs procedure used Chi-square test for testing differences in complication rates, length of stay and length of ventilation. Correlations between energy balances and complications was also be tested using one way analysis as well as ANOVA analysis between groups and within groups. Finally, post hoc tests were be performed to test multiple comparisons (energy balances and complications) and to try to group these parameters in homogeneous subsets using the method described by Scheff. Kaplan Meir curves assessed the proportion of patients free of infection in the 2 groups. Pothoff and Roy data from various covariance structures were used to evaluate the impact of daily changing variables on outcome. Omnibus test of model coefficients was used to evaluate if a specific variable showed an improvement over the baseline model using chi-square tests.

3. Results

Seven centers with a calorimeter available participated to the study. Due to a slow inclusion rate, the study was stopped after 6 years and after inclusion of only 417 patients. Figure 1 shows the inclusion flow chart. 4320 patients were not included because of not being ventilated, ventilated with high FiO2 or treated with inhaled nitric oxide, included in other studies, suffering head trauma, undergoing or after open heart surgery, or because of lack of available manpower, temporary lack of parenteral nutrition bags or temporary non access to indirect calorimetry. From the 417 intended to treat (ITT) patients, 13 were excluded because they were ventilated less than 48 h, 78 were discharged or died before day 3 (43 patients), and 29 were not able to be measured due to high FiO2. 332 completed the protocol (see Fig. 1). Table 1 shows the demographic characteristics of the 2 ITT groups. Study group patients received significantly higher energy and protein intake in most of the days (See appendix 4). Both groups had a negative daily energy balance and daily energy balance was signficantly more negative in the control group compared to the study group (Fig. 2). Moreover, the negative daily energy balance was stable during the first 14 days in the study group while it varied significantly in the control goup. The enteral products prescribed were as follow: Promote with and without fiber, Jevity, Nephrocare, Allitraq, Osmolite HN, Pulmocare, Glucerna, Periative, Oxepa (all form Abbott, USA), Peptamen, Impact and Nutren (Nestle), Nutrison multifiber, Isosource, Novasourse (Nutricia) and Fresubin HP (Fresenius Kabi). Parenteral nutrition used Baxter Oclinomel N9 with or without electrolytes to ensure a high protein intake together with the adequate energy administration to approach the target. When N9 was not available, Triomel N6 or N7 (Baxter, Chicago, Il, USA) was used. Non nutritional calories such as dextrose administration

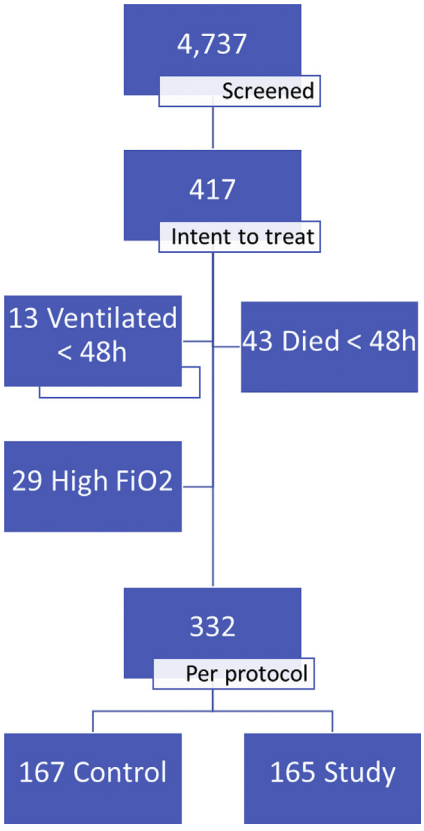

Fig. 1. Flow chart of the recruitment of the patients.

or propofol were significantly different between groups (Table 2) but did not reach excessive values, keeping the total energy administration below the measured energy expenditure and preventing from overfeeding. Tolerance to enteral nutrition was acceptable but gastric residual volume was higher in the study group without crossing 500 mL in most of the cases. Parenteral nutrition was used in 43 patients in the control group and 52 patients in the study group. Highest blood glucose levels were not significantly different between the two groups (see appendix 4). Insulin requirements were not significantly higher in the study group (72 ± 43 UI/d versus 48 ± 49 UI/d) (see Table 2).

3.1. Outcome

Infection as the primary outcome was not significantly decreased in the study group as compared to the control group (31 vs 40 new infections respectively). Secondary outcomes included mortality (Fig. 2), new complications, changes in daily SOFA scores (Appendix 4) did not reach significant differences for improvement. Hospital mortality shown on the Kaplan Meyer curve (Fig. 2), was decreased in the study group but this trend was not significant. Hazard ratios and coefficient Intervals are shown in Table 4 regarding various parameters. Receiving tight calorie control or more protein intake did not have a significant effect on survival. However, early extubation or weaning from the ventilator even after tracheostomy were associated with a significantly better outcome. Age and kidney failure were associated with a higher mortality. Variables such as age (below or above 60 years old), APACHE II (above and below 20) and BMI (below or above 25 or 30 kg/m2) added to energy intake variable did not impact outcome.

However, when including the daily energy balance parameters, hazard ratio (HR 0.0365, CI 1.00–1.00) became significantly lower in the study group, suggesting a strong influence of tight energy control. Protein administration was not found to be improving outcome (HR 1.003, CI 0.999–1007) (see Figs 3 and 4).

4. Discussion

The study group received significantly more energy, slightly more protein, and more propofol and dextrose 5% intravenously. Our study was not able to show any significant difference in the primary or secondary outcomes despite a difference in the energy

Table 1
Demographics and diagnosis/severity scores of the ITT (intent to treat) patients.

Parameters	Control ITT (n = 208)	Study ITT (n = 209)	P value	Control PP (n = 169)	Study PP (n = 170)	P value
Age (years)	60.7 ± 17.1	58.9 ± 18.0	0.30	60.4 ± 16.9	59.0 ± 18.4	0.47
Sex M/F	133/117	68/85	0.06	69/62	39/53	0.07
BMI kg/m2	28.4 ± 8.1	27.9 ± 7.6	0.54	28.6 ± 8.3	28.1 ± 7.8	0.68
SOFA admission	7.1 ± 3.1	7.4 ± 3.3	0.32	7.1 ± 3.1	7.5 ± 3.2	0.26
APACHE II admission	22.4 ± 7.0	22.2 ± 7.4	0.81	22.2 ± 6.9	22.1 ± 7.4	0.98

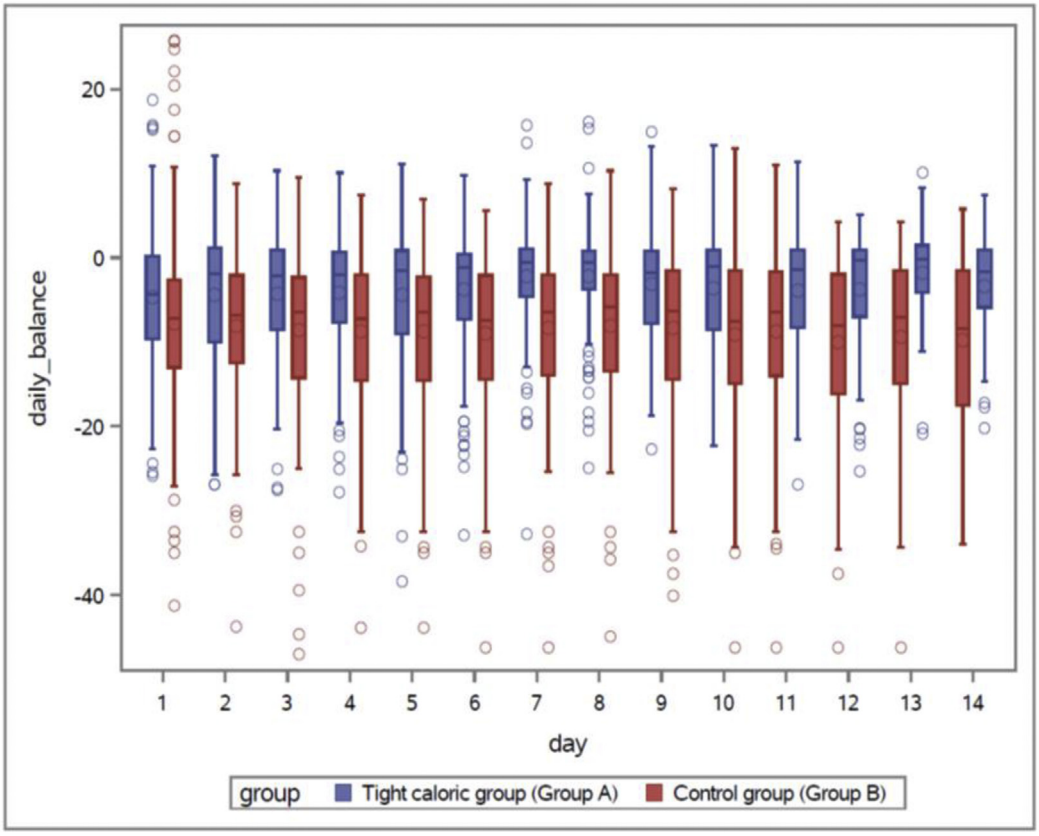

Fig. 2. Daily energy balances in the control and the study group. P < 0.0001. Daily balance is expressed in hundreds of kcal/d.

Table 2
Metabolic and nutritional parameters in the 2 groups per protocol. VO2 is oxygen consumption expressed in mL/min, VCO2 is CO2 production in mL/min, REE is resting energy expenditure in kCal/day and RQ is respiratory quotient.

Parameters	Control group PP	Study Group PP	P value
VO2 (mL/min)	270 ± 83	288 ± 91	0.67
VCO2 (mL/min)	226 ± 84	226 ± 66	0.50
RQ	0.81 ± 0.14	0.81 ± 0.15	0.14
Mean REE (kcal/d)	1942 ± 360	1953 ± 580	0.33
Mean Energy delivered/day (kcal/d)	1301 ± 535	1746 ± 755	0.04
Mean enterally delivered energy/day (kcal/d)	1062 ± 707	1139 ± 719	0.27
Mean parenterally delivered energy/day (kcal/d)	772 ± 643	1250 ± 502	0.02
Mean Protein prescribed (g/d)	105.0 ± 33.8	103.4 ± 32.5	0.56
Mean Protein delivered (g/d)	62.4 ± 33.9	77.3 ± 53.0	0.03
Mean daily energy balance (kcal)	−885 ± 535	−282 ± 896	<0.001
Propofol (kcal/d)	41 ± 15	137 ± 436	0.03
IV Dextrose (kcal/d)	31 ± 16	95 ± 89	0.003
Daily highly blood glucose (mg/dL)	148 ± 68	187 ± 59	0.16
Administered insulin (iu)	48 ± 49	72 ± 43	0.06

balance in favor of the study group. There was a trend towards decrease in the infection rate and mortality but these changes did not reach significance. The study was powered to include 560 patients and was stopped prematurely because of slow inclusion enrollment rate. This lower than expected number of recruited patients may explain the lack of significance. Our present study is different from the previous TICACOS study by several points. In this study, patients were not overfed, reaching progressively (in 4–5 days) to a mean of around 90% of the measured energy expenditure, even when including administration of non nutritional calories such as propofol and dextrose 5% in the study group. In the initial TICACOS study [1], the addition of non nutritional calories was not planned and therefore led to slight overfeeding (around 182 kcal/d). Length of ventilation, and the infection rate were not different between the two groups, as opposed to the previous study that showed an increase in these morbidity parameters in the study group probably related to overfeeding. In the current study, there was a significantly large daily calorie deficit reaching −874 ± 535 kcal/d in the control group (compared to the previous study −366 ± 432 kcal/d) and an acceptable deficit in the study group (−282 ± 895 kcal/d) as compared to the overfeeding observed balance of the pilot study (+186 ± 206 kcal/d). Previous studies have used indirect calorimetry for targeting energy intake. The SPN study [2] measured REE on day 3 to guide supplemental parenteral nutrition and found a decrease in infection rate. The adminstration of calories was progressive during the first 3 days. Petros et al. [3], in a small study including 100 patients measured only 37 of them using indirect calorimetry. The authors found a decrease in infection rate in the isocaloric group receiving energy according to REE. Finally the EAT-ICU study [4] was using IC for targeting energy prescription and nitrogen excretion for protein prescription in the study group did not reach a significant difference between the groups studied. It is remarkable that the energy and protein targets were reached in the first 24 h in thats study. In our study, this target was reached later (day 4–5), taking more in consideration the substrate endogenous production. In a large retrospective study published after the launch of this study, our group [11] observed that the best outcome in terms of mortality was when energy intake was around 70% of the measured energy expenditure. In the EAT ICU study, the control group received a 0.56 administered/REE ratio while the intervention group received 0.91 administered/REE ratio, suggesting that the two different calorie regimens would lead to the same effects on outcome. Our findings in that [12] suggested that there was no difference in mortality since the 2 groups were at the 2 extremes of the U curve observed in a large group of patients [11]. In our study, the administered/REE

Table 3
End points results. In ITT (intend to treat) and PP (per protocol) patients. VAP is ventilator associated pneumonia. ICU is intensive care unit.

Parameters	Control ITT	Study ITT	P value	Control PP	Study PP	P value
Infections Total	42/207	31/199	0.14	40/168	27/157	0.17
VAP	23/207	22/199	0.18	21/168	16/157	0.67
Renal complications	55/144	54/147	0.47	48/112	47/112	1.00
Liver	23/176	25/176	0.45	22/138	20/139	0.83
Respiratory	86/113	91/110	0.37	77/83	79/80	0.82
Need for new vasopressors	120/79	125/125	0.36	98/62	98/60	0.91
Need for surgery	31/168	36/165	0.31	29/131	31/128	0.77
Length of ventilation	9.8 ± 8.0	10.2 ± 9.3	0.40	11.7 ± 7.7	11.9 ± 9.2	0.84
Weaning yes no	99/100	113/89	0.23	75/85	86/74	0.26
Days in ICU	12.2 ± 8.9	13.1 ± 12.5	0.39	14.4 ± 8.6	15.3 ± 12.5	0.45
Extubation: yes/no	114/85	116/87	0.53	89/72	91/70	0.82
Reintubation Yes/no	30/169	29/174	0.89	29/131	27/134	0.77
Tracheostomy Yes/no	76/123	65/137	0.12	76/84	63/97	0.77
Days in Hospital	25.0 ± 16.0	26.8 ± 28.9	0.44	26.9 ± 16.2	31.0 ± 1.0	0.32
Discharged	197	159	0.99	127	131	0.89
To ward	118	131	0.30	91	104	0.26
To rehabilitation	24	20	0.52	23	20	0.62
To other hospital	8	4	0.25	8	4	0.25
Mortality ICU	46/207	45/199	0.91	36/163	33/165	0.68
Mortality 3 months	29/200	22/200	0.30	25/161	19/157	0.41
Mortality 180 days	7/198	8/199	0.14	6/159	8/156	0.59

Table 4
Variables in the Equation obtained by Omnibus test of model coefficients.

	P value	Estimate	Lower	Upper
Group	0.424	0.851	0.574	1.263
AGE	0.012	1.108	1.004	1.033
BMI >30	0.2		5.898	7.312
APACHE II	0.97	0.904	−1.805	1.757
ICU daysv	0.318	−1.202	−3568	1.164
Hospital Days	0.228	2.779	−8.862	2.114
LOV	0.658	0.949	−2.288	1.446
Extubation	0.0001	0.289	0.153	0.547
Reintubation	0.236	0.662	0.335	1.309
Requirement tracheostomy	0.0001	0.217	0.132	0.356
Weaning	0.002	0.416	0.239	0.722
Hepatic complications	0.304	1.315	0.780	2.216
Respiratory complications	0.176	1.343	0.876	2.058
Kidney complications	0.001	2.228	1.379	3.600
Noradrenaline use	0.503	1.200	0.704	2.045
Total energy	3.515	1.000	1.000	1.000
Protein	1.617	1.003	0.999	1.007
Daily Balance	4.372	0.0365	1.000	1.000

ratios were quite similar, mean administered/REE ratio in the control group was 0.67 and was 0.89 in the study group. Like in the EAT ICU study, this may explain the results. In addition, our study shows that it is difficult to tightly control energy intake since REE varies significantly daily. However, the daily calorie balance was stable in the study group. There was a nonsignificant trend towards decreased mortality in the study group. This improvement may be related to the increased protein administration in the study group, but this was not confirmed by the adjusted mortality analysis. Weijs et al. [12] showed that protein intake may have a more powerful impact on outcome than reaching an energy target in a retrospective study. Nicolo et al. [13] and Compher et al. [14] in other retrospective studies showed that the most significant parameter affecting survival was the amount of protein prescribed. Our study underlines the difficulties to separate the divergent effects of protein and energy on outcome in the critically ill patient.

4.1. Measurements of energy expenditure, administration of propofol and D5W

It is remarkable to observe a not significantly different measurement of energy expenditure between the 2 groups. However, a significant day to day variation was observed ($p < 0.03$), stressing the importance of daily measurements. Others have observed this variation [15–17] and stressed the fact that one measurement may not be sufficient for the duration of the ICU stay. In addition, non nutritional calories (NNC) have to be recorded and in our study, the amount of propofol and dextrose administration was significantly higher. However, these differences did not reach levels observed in other studies. Propofol doses were 41 ± 15 kcal/d in the control group and 137 ± 436 kcal/d in the study group and D5W administration was 31 ± 16 kcal/d versus 95 ± 89 kcal/d in the study group. A NCC of 226 kcal was observed in the study group. Devaud et al. [18] already pointed out the risk of administration of large doses of propofol by affecting the energy balance. Bousie et al. [19] found 142 patients out of 146 with NNC median value of 580 kcal (interquartile range 310–1043 kcal). Weijs et al. [20] described that NNCs comprised 7.9% (132 kcal/d) of total energy intake (6.4% in overfed patients vs 10.1% in non-overfed patients) in his observed patients.

4.2. Protein intake

Protein administration in the 2 groups was different than in the previous study [1]. In the present study mean administered protein over the 14 days was of 77 ± 53 g/d in the study group versus 66 ± 34 g/d in the control group, compared to 76 ± 16 g in the study group and 53 ± 16 g/d in the control group in the past TICACOS pilot study. This improvement of protein administration in the control group may be explained by the improved protein enriched commercial products used. Protein administration varied from day to day ($p < 0.001$) and was significantly different between groups ($p < 0.03$), but the differences were observed mainly after day 5 (see Fig. 3 and appendix 4). Initial protein administration was not different between the groups, related to the progressive administration of calories progressing from 1310 ± 610 kcal/d at day one to 1657 ± 746 kcal/d at day 7 for the study group and from 1342 ± 519 kcal/d to 1463 ± 593 kcal/d in the control group ($p = 0.04$ compared to study group) at day 7. Only observational studies [11,13,14,20,21] and some prospective randomized studies [22,23] suggest that increased protein intake improves outcome. The effect of protein on outcome in ICU patients is not clear. Even if larger doses (1.3 g/kg/d) of protein are recommended, most of the studies [2,24,25] reported lower intakes not exceeding 1 g/kg/d, as in our study. The EAT ICU study [4] was successful in administrating higher protein intake, but failed to show a significant difference. Our study was not targeted to administer high protein intake, but

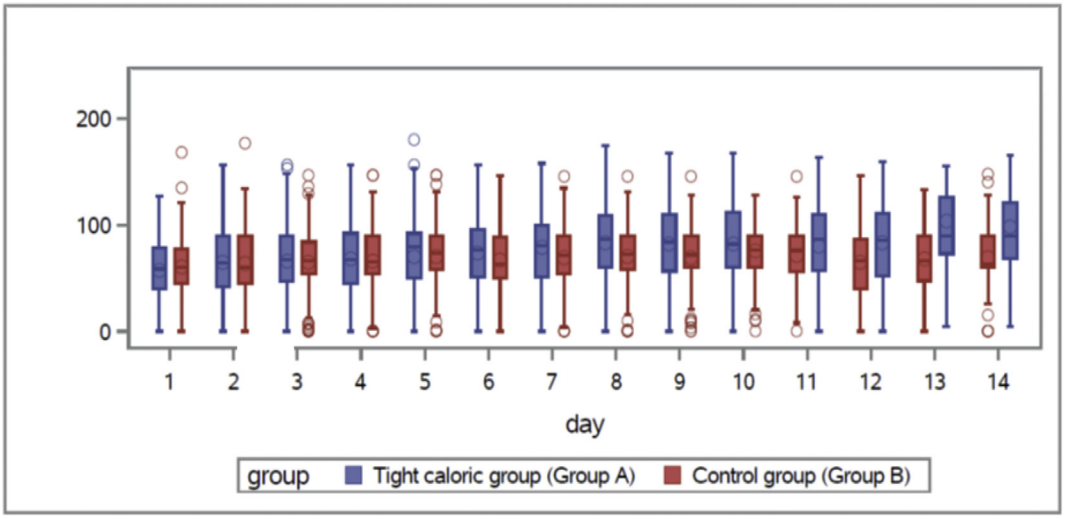

Fig. 3. Protein administration in the control and the study group ($p < 0.03$).

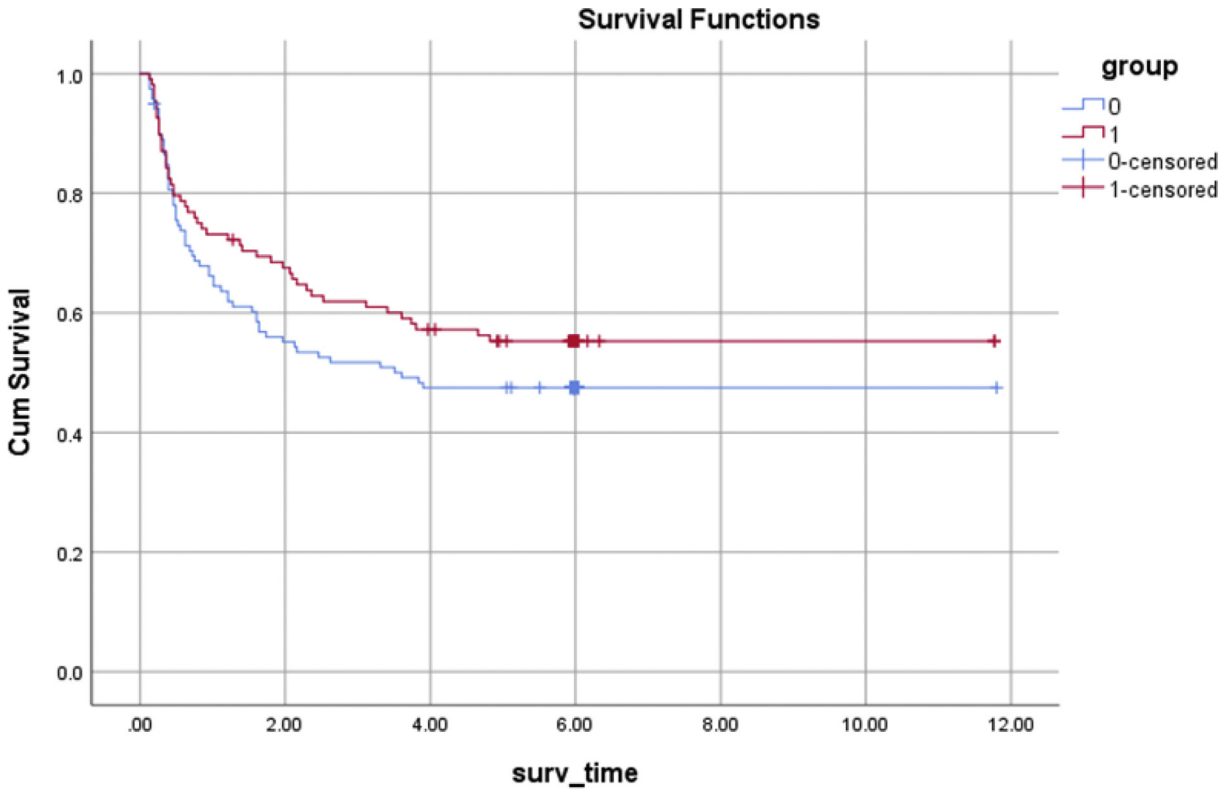

Fig. 4. Kaplan Meyer curb for survival in the Intent to treat patients.

due to the administration of increased calories though formulas, protein intake was also relatively increased.

4.3. Glucose control and insulin

The highest glucose levels were larger in the study group as well as the daily insulin requirements. These differences did not reach significance. They may be explained by an increase in carbohydrates in the study group. These highest glycemia levels were associated with increased daily insulin administration (48 ± 49 ui/d in the control group versus 72 ± 43 ui/d in the study group). Numerous studies have observed a lower insulin requirement associated with lower calorie intake [26–28]. However, as opposed to other studies [29,30], in our study the lower level of insulin administration was not associated with a lower infection rate.

4.4. Gastric residual volume and enteral feeding tolerance

Interestingly, mean gastric residual volumes were comparable between the 2 group: 168 ± 332 in the control group vs 289 ± 461 mL in the study group (NS), allowing enteral nutrition in most of the patients. There was no overfeeding by enteral feeding and if gastrointestinal failure occurred, energy target was completed by parenteral nutrition. This approach is different from the NUTRIREA 2 (25) where patients were receiving the all energy target enterally or parenterally integrally. When enteral nutrition was not feasible in our study, parenteral nutrition was prescribed preventing underfeeding.

4.5. Limitations and strengths of the study

Our study has limitations since it was stopped without reaching the required recruitment. Trends for improvement was observed, but significance was not reached. However, our study had many strengths: indirect calorimetry was measured several times, overfeeding was avoided, NNC was taken into account, severe hyperglycemia was prevented, and mainly the nutrition intake was performed progressively. Our study also points out that daily requirements and administration differ significantly and a stable continous administration of calories like in the TARGET study [31] do not respecting these variations. However, our study underlines the difficulties to adapt to these requirements and mainly to pair the administration of energy and protein.

5. Conclusions

This multicenter prospective randomized control study failed to recruit enough patients and did reach a not significant decrease in infection rates and mortality in the patients receiving tight calorie control. As opposed tothe TICACOS pilot study, patients were not overfed even when non-nutritional calories were taken into account. No increase in length of stay or infection was observed. These results together with other prospective randomized studies using indirect calorimetry might give a signal towards improved survival when patients' medical nutritional therapy is guided by indirect calorimetry.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.05.024.

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