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ORIGINAL RESEARCH INTENSIVE CARE

Role of recombinant human growth hormone in weaning of prolonged ventilation after major abdominal cancer surgeries; open-label, placebo-controlled, randomized trial

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Abstract

Objective: The use of recombinant human growth hormone (rhGH) in difficult to wean patients with prolonged ventilation periods may increase the likelihood of weaning and thus reduce the mechanical ventilation time. This placebo-controlled randomized study aimed to assess the efficacy of rhGH on the weaning of prolonged mechanical ventilation.

Study Design: The study was conducted in the National Cancer Institute, Cairo, Egypt, from March 2018 to August 2018. Enrolled patients (60) were randomized to the GH group and the control group, 30 in each group. Before randomization, the same management was offered to both groups. After randomization, in the GH group, patients received 4 IU rhGH IM, twice per day for ten days. In the control group, patients received placebo injections (saline) at the same intervals and conditions with the continuation of the regular ICU management given to both groups. The primary outcome measurement was the proportion of patients weaned in both groups.

Results: There was no statistically significant difference ($P > 0.05$) between the two groups regarding their baseline data in terms of age, BMI, and gender. Ventilation days were significantly lower in the GH group than in the control group; 33.20 ± 16.57 vs. 48.73 ± 10.66 days ($P < 0.001$). The number of failed-to- wean patients was significantly lower in the GH group than the control group [10 (33.33%) vs. 22 (73.33%); ($P = 0.002$)]. The odds ratio (OR) was 0.18 (95% CI: 0.06-0.55), the Absolute Risk Reduction (ARR) was 0.4 (95% CI: 0.17-0.63) and the Number Needed to Treat (NNT) was 2.5 (95% CI: 1.58-5.93). In addition, the study showed no significant differences between the GH group and the control group concerning the blood pressure, blood sugar. During the study period, there was no statistically significant difference between groups as regards the incidence of ventilator-associated pneumonia (VAP) or the number of deaths.

Conclusion: The use of rhGH in cases difficult-to-wean patient with prolonged ventilation period increases the likelihood of weaning and reduces the mechanical ventilation time.

Abbreviations: rhGH - Recombinant human growth hormone BMI – Body mass index; NNT - Number Needed to Treat; ARR - Absolute Risk Reduction; VAP - ventilator-associated pneumonia; PPC - Postoperative pulmonary complication; RSBI - rapid shallow breathing index; HIPEC - Hyperthermic intraperitoneal chemotherapy

Clinical Trial Registration: NCT03717168: clinicaltrials.gov/ct2/show/NCT03717168

Key words: Growth hormone; rhGH; prolonged mechanical ventilation; respiratory failure; VAP

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1. Introduction

Postoperative pulmonary complications (PPCs) after major abdominal surgeries are common and can cause substantial morbidities and mortalities. The grades of PPC can range from minor abnormal postoperative course to multiple organ failure. Besides, acute respiratory insufficiency can occur in 3%-27.4% of cases with its subsequent impact on survival and pose an economic burden due to the prolonged hospital stay and high patient costs.[1-4]

In those type of patients, deteriorations in the pulmonary functions may occur in the form of reduced lung volumes, atelectasis, and alveolar collapse. Ventilation-perfusion mismatch, with its subsequent hypoxemia, can occur.[5]

After reporting about 37 definitions[6] to the prolonged mechanical ventilation, it is defined by the Medicaid and Medicare in the USA as higher than 21 days of mechanical ventilation.[7]

In addition to the many critical complications of mechanical ventilation, including pneumothorax and complications of tracheostomy, difficult weaning with all its underlying causes remains a problematic issue in those cases. The criteria of readiness for weaning trial had identified many criteria that can help in the decision of weaning both subjective or objective assessments and most importantly, the criteria of adequate oxygenation like the rapid shallow breathing index (RSBI) and the oxygenation index.[8-12]

The recombinant human growth hormone (rhGH) is a synthetic metabolic hormone that improves the synthesis of protein and corrects hypoalbuminemia. It also enhances wound healing and supports the recovery of respiratory muscle function. When used for weaning from mechanical ventilation, it reduces the mechanical ventilation time, ICU-admission period. Moreover, it decreases the incidence of ventilator-associated pneumonia (VAP) & ICU mortality.[13-15]

One case report study presented a patient with prolonged ventilation with failure of weaning after 42 days. After receiving rhGH for 20 days, the patients showed improvement of the protein metabolism as well as the strength of respiratory muscles; the patient was weaned successfully on the 75th postoperative day.[16]

The efficacy and safety of rhGH in promoting respiratory independence in cases with postoperative respiratory failure have been supported by one study upon 53 patients. The study showed that 81% of the previously non-weanable patients were eventually weaned from mechanical ventilation.[17]

The rationale intended for this open-label, placebo-controlled randomized study was to assess the efficacy of the use of rhGH on increasing the incidence of weaning of prolonged mechanical ventilation cases after abdominal cancer surgery and reduction of the mechanical ventilation time.

2. Methodology

This parallel randomized-controlled trial was conducted in the National Cancer Institute, Cairo, Egypt, during the period from March 2018 to August 2018. The study adopted the principles of the Declaration of Helsinki and following the Medical Research Involving Human Subjects Act (WMO), and was approved by Institutional Review Board (IRB Number 201617030.2P) and Clinical trial registration no (ClinicalTrials.gov Identifier: NCT03717168). The purpose of this study was explained to the legal closest relative of all subjects before their enrollment to the study, and an informed consent form was signed by and obtained.

ASA I/II patients aged >18 years who underwent major abdominal cancer surgery; e.g. gastrectomy, colectomy, partial hepatectomy, Whipple's operation, hyperthermic intraperitoneal chemotherapy (HIPEC) etc. and needed postoperative ICU admission and mechanical ventilation with or without tracheostomy and could not be weaned from the ventilation after more than 21 days were included to the study.

The followings were excluded from the study: those with history of chronic cardiac, renal or respiratory illness, septic or septic shock patients on inotropic supports, not fully alert/conscious patients, or ASA III or IV. In addition, patients who underwent thoraco-abdominal surgeries, patients weaned from MV and re-intubated and ventilated again for less than 21 days even if the total time of ventilation in the two times is more than 21 days, were excluded.

Procedures:

Before randomization, the same procedures were applied to both groups. Patients who underwent major abdominal surgery and required postoperative mechanical ventilation were managed as usual until the 21st day of mechanical ventilation including the same antibiotics protocol, same enteral/parenteral nutrition protocols, sedation and same anticoagulant (anti-VTE) protocol. If

they could not be weaned, they underwent tracheostomy in the operating theatre by senior specialized surgeons under inhalational anesthesia using sevoflurane and local infiltration of lidocaine 1% on the 22nd day. After the establishment of tracheostomy, mechanical ventilation was resumed in the ICU by the same parameters before it.

Randomization and blinding:

Random numbers list was generated by the computer to be used for the allocation of the participants by the biostatistician. In the 22nd day of mechanical ventilation, the legal closest relatives for patients who met inclusion criteria were approached for informed consent for study enrollment. Once consent was obtained, patients were randomized using the random table into two groups (30 patients each) with an allocation ratio of 1:1. The study was open-label placebo-controlled study.

Intervention:

After randomization, in the study group, patients received 4 IU rhGH (*Saizen, Switzerland, Serono Products*) IM, twice a day for ten days. In the control group, patients received placebo injections (saline) at the same intervals and conditions with the continuation of the regular ICU care given to both groups.

Weaning from mechanical ventilation was managed to all patients of both groups by the same protocol applied by the ICU team where patients requiring less than 50% inspired oxygen and positive end-expiratory pressure <10 cmH_2O were given trials for spontaneous breathing and were extubated if there were no tachypnea (respiratory rate <30), hypoxia, or hypercarbia.

Laboratory investigations were done at the following intervals: blood glucose, complete blood count (CBC) every 24 hours. ABG every 12 hours. Serum albumin, creatinine, liver function tests, and coagulation profile every three days. Chest x-ray was done daily. Total parenteral nutrition was given to all patients in the form of 35 kcal/kg/day (70% carbohydrates / 30% lipids with 2gm/kg/day proteins).

Outcome measures:

The primary outcome measurement was the proportion of patients weaned in both groups. The secondary outcome measurements were the mechanical ventilation duration (in days), the patients' hemodynamics, the oxygenation index (OI = (FiO_2×mean airway pressure)/PaO_2) interpreted as ; 0 to 25 indicating good outcome, 25 to 40 chance of death >40% while 40 to 1000, extracorporeal membrane oxygenation (ECMO) to be considered, the Rapid Shallow Breathing Index (RSBI) [the ratio of respiratory frequency to tidal volume (f/VT)], incidence of VAP and ICU mortality.

Statistical analysis and sample size justification:

We assume that the utilization of rhGH will increase the proportion of weaned patients by 50%. Thus, with significance level $\alpha = 0.05$ and 80% power ($\beta = 0.2$), 22 patient patients had to be recruited in each group. To account for any dropouts, we identified 30 patients in each group; thus, the total sample needed is 60 patients.

All statistical tests were made using a significance level of 95%. SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc., Chicago, IL, USA) was used for the statistical analyses. Data were summarized by the mean, standard deviation in

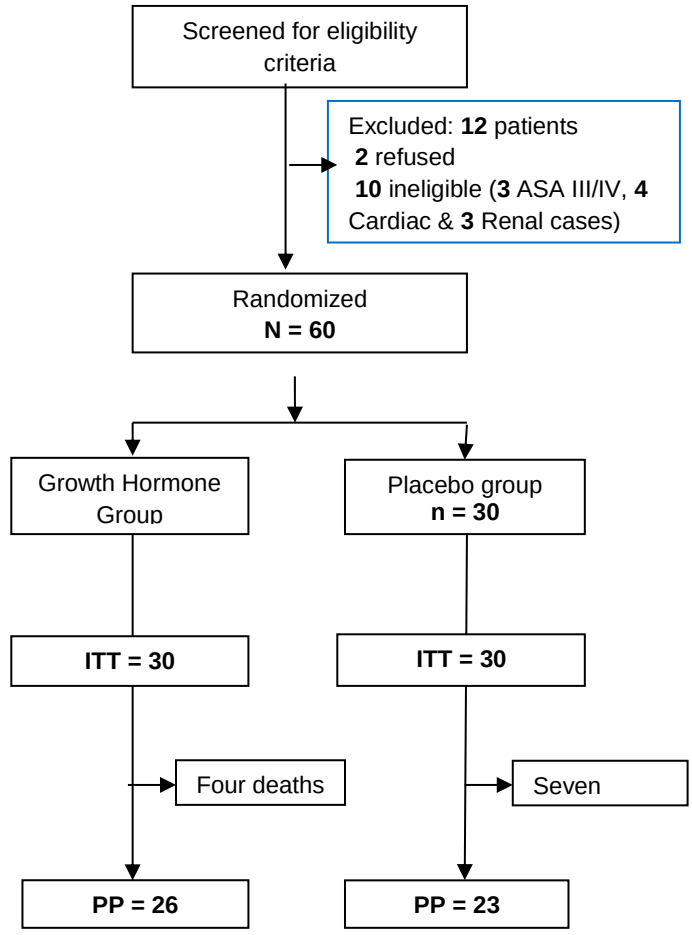

Figure 1: Consort flow chart

numerical data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the student t-test after testing for normality. For comparing categorical data, a Chi-square test was applied. The statistical analyses were made upon the intent-to-treat population (ITT).

For the analysis of the primary outcome variable, we calculated the relative risk (RR) with 95% confidence interval, the absolute risk reduction (ARR), the relative risk reduction (RRR) and the number needed to treat (NNT). $P < 0.05$ were considered as statistically significant.

3. Results

The legal closest relatives for all patients (72) who were under prolonged mechanical ventilation (failed-to- be-weaned patients) for more than 21 days were asked to sign the informed consent for study enrollment. Two of them refused to participate, and ten did not meet the eligibility criteria (3 ASA III or IV, 4 were cardiac patients, and three were with end-stage renal disease). Enrolled patients (60) were randomized to the growth hormone group and the control group, 30 in each group.

The statistical analysis was done according to the ITT population. The dispositions of these subjects are shown (Figure 1).

Baseline characteristics:

There was no statistically significant difference ($P > 0.05$) between the two groups regarding age, BMI, and gender (Table 1). The patients' age was 58.23 ± 11.22 years in the GH group and 60.03 ± 10.49 years in the control group ($P = 0.559$). More than 50% of patients in both groups was of male gender ($P = 1$).

Blood pressure:

Results indicated no significant ($P > 0.05$) differences between the GH group and the control group concerning the systolic and diastolic pressure measurements along the study follow-up period (8 weeks), as shown in Table 2.

Blood sugar:

Results indicated no significant ($P > 0.05$) differences between the GH group and the control group concerning the blood sugar measurements along the study follow-up period (8 weeks), as shown in Table 3.

Table 1: Comparative demographic data in the groups

Parameters	Growth hormone group	Control group	P-value
ITT population	N=30	N=30	
Age (years), mean ± SD	58.23 ± 11.22	60.03 ± 10.49	0.559
BMI (Kg/m^2), mean ± SD	28.47 ± 5.48	28.70 ± 6.23	0.213
Gender, number (%)			
Male	17 (56.67)	16 (53.33)	1.00
Female	13 (43.33)	14 (46.67)	

Table 2: Blood pressure changes in both groups

Period	Diastolic blood pressure mmHg mean ± SD			Systolic blood pressure mmHg mean ± SD		
	GH Group	Control Group	p	GH Group	Control Group	p
Base line	65.97 ± 9.66	68.47 ± 8.98	0.67	123.73 ± 12.13	119.40 ± 13.55	0.40
Week 1	67.57 ± 9.36	65.80 ± 9.85	0.43	122.63 ± 4.78	121.57 ± 6.19	0.17
Week 2	74.47 ± 10.97	70.93 ± 8.12	0.08	121.70 ± 9.17	116.20 ± 11.98	0.12
Week 3	71.53 ± 10.18	73.24 ± 9.85	0.94	124.67 ± 8.15	120.48 ± 8.89	0.52
Week 4	73.00 ± 9.14	70.24 ± 10.89	0.28	125.10 ± 10.32	126.03 ± 12.17	0.13
Week 6	72.68 ± 11.71	76.93 ± 10.61	0.79	128.79 ± 7.92	125.00 ± 9.37	0.36
Week 8	73.30 ± 8.90	67.09 ± 10.89	0.49	122.89 ± 5.13	125.30 ± 6.14	0.14

Table 3: Blood sugar measurements in both groups

Period	GH Group mean ± SD	Control Group mean ± SD	p
Base line	119.97 ± 11.40	122.90 ± 12.11	0.76
Week 1	117.70 ± 6.69	116.63 ± 8.84	0.07
Week 2	121.70 ± 9.22	117.73 ± 7.17	0.19
Week 3	121.50 ± 9.52	119.55 ± 7.73	0.23
Week 4	125.13 ± 13.83	119.45 ± 12.47	0.89
Week 6	122.21 ± 11.09	125.70 ± 15.04	0.16
Week 8	137.44 ± 12.65	132.35 ± 15.70	0.26

Table 4: Ventilation days and failure of weaning

Parameter	GH Group	Control Group	P value
Intent to treat population	30	30	
Ventilation days, mean ± SD	33.20 ± 16.57	48.73 ± 10.66	< 0.001
Weaned patients, n (%)	20 (66.67%)	8 (26.67%)	0.002
Failed to be weaned	10 (33.33%)	22 (73.33%)	
Estimate	**Point estimate**	**95% Confidence interval**	
Odds ratio (OR)	0.18	0.06-0.55	
Relative risk (RR)	0.45	0.26-0.79	
Relative risk reduction (RRR)	0.55	0.21-0.74	
Absolute risk reduction (ARR)	0.4	0.17-0.63	
Number needed to treat (NNT)	2.5	1.58-5.93	

Ventilation days and failure of weaning and indices of respiratory failure:

Ventilation days were significantly ($p < 0.001$) lower in the GH group (33.20 ± 16.57 days) than in the control group (48.73 ± 10.66 days). The number of failed-to-be-weaned patients was significantly ($P = 0.002$) lower in the GH group, ten patients (33.33%) than the control group 22 patients (73.33%). The odds ratio (OR) was 0.18 (95% CI: 0.06-0.55), the ARR was 0.4 (95% CI: 0.17-0.63) and the NNT was 2.5 (95% CI: 1.58-5.93).

During the first four weeks of the study, there was no significant difference in the oxygenation index ($P > 0.05$) between both groups. However, starting from week 6,

Table 5: Parameters of respiratory failure

Period	Oxygenation index			RSBI		
	GH Group	Control Group	p	GH Group	Control Group	p
Base line	31.00 ± 4.11	29.30 ± 6.63	0.25	164.40 ± 23.30	166.37 ± 25.89	0.43
Week 1	32.90 ± 2.61	33.97 ± 3.54	0.54	171.77 ± 18.40	181.03 ± 21.83	0.33
Week 2	31.63 ± 3.07	31.53 ± 2.37	0.19	148.70 ± 16.16	159.63 ± 23.73	0.07
Week 3	28.80 ± 2.20	29.10 ± 2.56	0.20	139.80 ± 19.31	144.21 ± 24.31	0.60
Week 4	19.23 ± 5.17	29.59 ± 8.21	< 0.001	99.67 ± 15.18	151.90 ± 40.73	< 0.001
Week 6	14.75 ± 4.86	32.89 ± 8.72	0.02	87.18 ± 21.04	151.33 ± 46.59	< 0.001
Week 8	12.70 ± 4.33	31.74 ± 6.20	0.02	68.07 ± 23.78	141.13 ± 4.58	< 0.001

there was a highly significant ($p < 0.001$) difference in the oxygenation index between both groups with higher levels in the GH group (Table 5).

The same also was noticed during the first four weeks of the study, there was no significant difference in the RSBI ($P > 0.05$) between both groups. While starting from week 6, there was a highly significant ($P < 0.001$) difference between both groups with lower levels in the GH group (Table 5).

Survival and VAP

During the study period, there was no statistically significant difference between groups as regards the incidence of VAP or the number of deaths. However, the incidence of VAP was lower ($P = 0.605$) in the growth hormone group 13 (43.33%) than the control group 16 (53.33%). In addition, the number of deaths was lower ($P = 0.505$) in the growth hormone group four (13.33%) than the control group 7 (23.33%).

4. Discussion

This parallel open-label placebo-controlled randomized-controlled trial showed a statistically and clinically significant difference in the number of mechanical ventilation (MV) days and weaning from MV as well as the indices of respiratory failure between both the GH group and the control group.

Ventilation days were significantly lower in the GH group than in the control group. The number of failed-to-be-weaned patients was significantly lower in the GH group than in the control group. There was a highly significant difference in the oxygenation index between both groups with higher levels in the GH group starting from the sixth week. In addition, starting from week 6, there was a highly significant difference in the RSBI between both groups with lower levels in the GH group. Moreover, this study indicated no significant differences between the GH group and the control group concerning the systolic and diastolic pressure measurements as well as blood sugar levels along the study follow-up period (8 weeks).

Besides, there was no significant difference between groups as regards the incidence of VAP or the number of deaths.

The results of the current study showed a significant increase in the proportion of patients with successful weaning in the group received growth hormone. These results are in accordance with the results of an uncontrolled prospective study examined the effects of growth hormone, which showed successful weaning in more than 80% of cases.[17]

The number of MV days was significantly lower in the growth hormone groups versus the control group in the current research study.

That is in disagreement with the results of a small prospective, randomized, placebo-controlled trial where the authors showed no shorter duration of ventilatory supports.[18]

The safety profile of the therapeutic utilization of recombinant growth hormone was developed over the years, and it has shown it to be a very safe hormone with few adverse events. However, when it was used in critically ill patients with respiratory failure, the mortality rate was significantly higher in the GH group than in the placebo group. Thus, it was recommended not to treat those patients with GH, especially whenever there is an active infection. In an investigation of these research studies, it was clear that they used GH in the acute phase of the critical illness with a high dose (16-24 IU per day). In the current study, a dose of 8 IU of GH per day was used for patients with prolonged MV (>21 days) who were in the chronic phase of their illness.[19-21]

Even though the results of the current study showed no significant difference in the blood pressure or the blood glucose between both groups, intensive monitoring of blood pressure and blood glucose should be considered to prevent hypertension and hyperglycemia.

In light of these data mentioned above about the safety and mortality of GH, selection of cases with specific criteria regarding the phase of the critical illness and dosage is necessary before employing the utilization of GH.[21-23]

This current study is well-designed, randomized controlled study with enough sample size, and its results come from the intent-to-treat population.

5. Conclusion

In conclusion, the use of rhGH in difficult-to-be-weaned patients with prolonged ventilation period may increases the likelihood of weaning and reduces the mechanical ventilation time.

6. Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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8. Authors' contribution

All authors shared the idea, data collection, statistical analysis, writing and reviewing the manuscript of this study.

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