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Critical Rounds

MICRO LABS LIMITED

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RECOVERY: Steroid Benefit Holds Up in Severe COVID-19

The sickest patients diagnosed with COVID-19 who obtained dexamethasone, the low-cost steroid, have a slightly lower risk of mortality compared with patients receiving standard care, preliminary results from the UK-based RECOVERY trial.

Martin Landray, PhD, on behalf of the RECOVERY Collaborative Group, and colleagues reported that the rate of mortality was slightly smaller among patients in the dexamethasone community who provided mechanical ventilation than those providing routine treatment (29.3% vs. 41.4%; RR 0.64; 95 % CI 0.51-0.81) and those obtaining artificial oxygen without mechanical ventilation (23.3% vs. 26.2%; RR 0.82; 95 % CI 0.72-0.94).

However, there was no substantial change in the rate of mortality for those patients who did not provide respiratory assistance (17.8% vs. 14.4%; RR 1.19; 95 % CI 0.91-1.55), the Landray community wrote in the New England Review of Medicine. Researchers observed that average 28-day mortality in the dexamethasone community was slightly smaller than normal treatment (22.9 percent vs. 25.7 percent, RR 0.83, 95 percent CI 0.75-0.93, P<0.001).

Those are not fresh findings, with the UK-based COVID-19 Therapy Randomized Assessment (RECOVERY) investigators reporting preliminary topline data in a press release on June 16th. The prosecutors claimed, back in June, that they will apply their evidence for peer examination.

Commenting on the outcome of the June news conference at last week's COVID-19 meeting of the International AIDS Society, National Institute of Allergy and Infectious Diseases (NIAID) Administrator Anthony Fauci, MD, described the outcomes of the topline as very promising for individuals on oxygen-needing ventilators. He said that's very important because it goes hand in hand with exactly what we know about pathogenic mechanisms, mainly that you really want to block the virus early on, but keep the immune system intact and then, when you have an aberrant inflammation, you want to dampen that.

Fauci said dexamethasone was now recommended by the NIH group of clinical guidelines for COVID-19 patients who meet the specific criteria used in the study due to decreased mortality, based on the topline results. In certain ways it is now becoming the norm of treatment on ventilators for elderly patients and/or needing oxygen.

Fauci has wrote a NEJM editorial preceding H. Clifford Lane, MD, also from the NIAID, reports that the latest results on dexamethasone are bringing insight to an field of medical confusion that would undoubtedly contribute to more lives being saved. Landray and collaborators analyzed results in 176 public health care agencies around the UK for people diagnosed with COVID-19. If patients had reported or suspected COVID-19 infection, they were free. Originally limited to patients aged 18 and over, the age restriction was abolished on May 9 and people became considered for both pregnant and breast feeding. The primary outcome was death in all-cause within 28 days in randomisation.

In total, 2,104 patients were randomized to receive intravenous dexamethasone (6 mg daily), while 4,321 patients received regular care. They were around 66 average age, and women or girls were 36 per cent. Less than half have at least one medical comorbidity, with coronary failure at 27 percent, asthma at 24 percent and chronic lung disease at 21 percent. At randomization, 16 percent got artificial ventilation, 60 percent still got oxygen and 24 percent did not receive any. Nearly all participants in the dexamethasone community obtained at least one injection of the medication, and the mean treatment period was seven days. Nevertheless, as part of their diagnosis, 8 per cent of patients in the normal treatment category have obtained dexamethasone. About a quarter of patients in each group received azithromycin during the follow-up period.

Landray and colleagues observed that there was also a significant advantage in patients hospitalized more than 7 days after symptom initiation when inflammatory lung disease is expected to be more severe as well as gain in the sickest patients. The dexamethasone community often saw a shorter mean period of hospitalization than normal treatment (12 days vs. 13 days) and a better chance of being released alive after 28 days, with the strongest benefits observed in patients requiring mechanical ventilation after randomisation.

Lane and Fauci said this study shows that "rigorous clinical testing" can be performed during a pandemic, equivalent to the massive randomized experiment undertaken in the Democratic Republic of the Congo during the 2019 Ebola epidemic. In the earlier Ebola epidemic in West Africa, the PALM analysis identified two successful treatments for Ebola in a far more convincing manner than smaller studies.

Lane and Fauci wrote that it is our duty to quickly plan, introduce and complete studies of the most effective therapeutic agents and vaccines against this disease within the global medical research group.

Source: The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 -- Preliminary report. N Engl J Med 2020; DOI: 10.1056/NEJM0a2021436.

Effect of Colchicine Vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in COVID-19

INTRODUCTION

During the first quarter of 2020, extreme acute respiratory coronavirus syndrome 2 (SARS-CoV-2) outbreak developed into a global pandemic. Early results showed that coronavirus disease 2019 (COVID-19) contributes to an extreme immune reaction that primarily affects the respiratory tract, contributing in some instances to severe lung infection or acute respiratory distress syndrome. Potentially effective applicants for therapy under this pathophysiological context would have active anti-inflammatory activity without the negative consequences of steroids and non-steroidal anti-inflammatory drugs. Colchicine has traditionally been used for the treatment of gout and rheumatism,

And a number of studies in recent years have shown a favorable safety-benefit profile among cardiovascular disease patients, including pericarditis. Colchicine's anti-inflammatory action is mediated by entirely different pathophysiologic routes than corticosteroids and NSAIDs. In addition, colchicine inhibits neutrophil chemotaxis and activity in response to vascular injury, inhibits inflammasome signaling and reduces the production of active interleukin-1β, reduces neutrophil-platelet interaction and aggregation, and has rapid onset of anti-inflammatory effects when the standard oral regimen of colchicine used for gout flares (1.2 mg initially followed by 0.6 mg every hour for 6 hours or until severe gastrointestinal symptoms occur) is followed.

These features indicate that colchicine can balance anti-inflammatory activity with an appropriate safety profile, contributing to the possibility that COVID-19 may be a secure and efficient alternative for anti-inflammatory care. In the present research, the investigators tried to determine colchicine 's capacity for enhancing results in COVID-19 hospitalized patients.

METHODS

DESIGN, SETTING, AND PARTICIPANTS: In this prospective, open-label, randomized clinical trial (the Greek Study in the Effects of Colchicine in COVID-19 Complications Prevention), 105 patients hospitalized with COVID-19were randomized in a 1:1 allocation from April 3 to April 27, 2020, to either standard medical treatment or colchicine with standard medical treatment. The study took place in 16 tertiary hospitals in Greece.

INTERVENTION Colchicine administration (1.5-mg loading dose followed by 0.5mg after 60 min and maintenance doses of 0.5 mg twice daily) with standard medical treatment for as long as 3 weeks.

MAIN OUTCOMES AND MEASURES

Primary end points were:

(1) maximum high-sensitivity cardiac troponin level;

(2) time for C-reactive protein to reach more than 3 times the upper reference limit; and

(3) time to deterioration by 2 points on a 7-grade clinical status scale, ranging from able to resume normal activities to death.

Secondary end points were:

(1) the percentage of participants requiring mechanical ventilation,

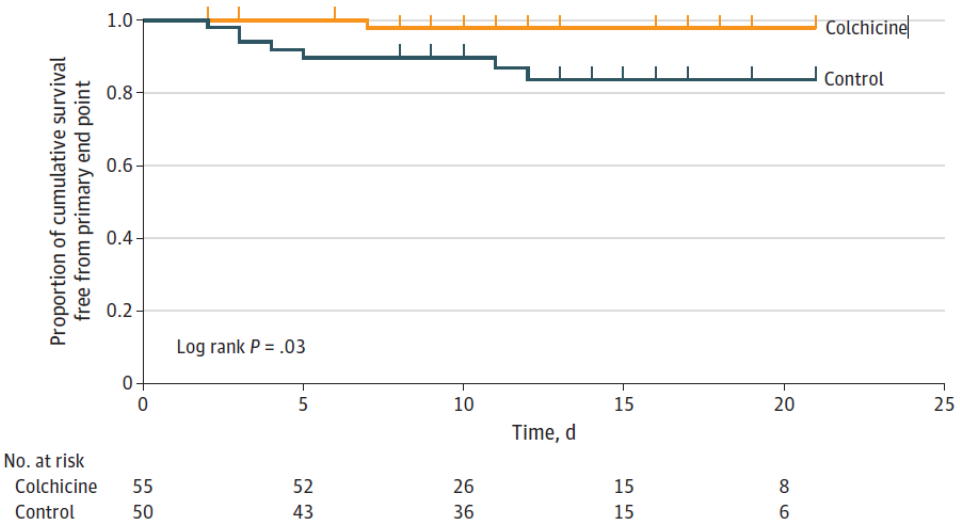
(2) all-cause mortality, and

(3) number, type, severity, and seriousness of adverse events.

The primary efficacy analysis was performed on an intention-to- treat basis.

RESULTS

A total of 105 patients were evaluated (61 [58.1%] men; median [interquartile range] age, 64 [54-76] years) with 50 (47.6%) randomized to the control group and 55 (52.4%) to the colchicine group. Median (interquartile range) peak high-sensitivity cardiac troponin values were 0.0112 (0.0043-0.0093) ng/mL in the control group and 0.008 (0.004-0.0135) ng/mL in the colchicine group (P = .34). Median (interquartile range) maximum C-reactive protein levels were 4.5 (1.4-8.9) mg/dL vs 3.1 (0.8-9.8) mg/dL (P = .73), respectively. The clinical primary end point rate was 14.0% in the control group (7 of 50 patients) and 1.8%in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95%CI, 0.01-0.96; P = .02). Mean (SD) event-free survival time was 18.6 (0.83) days the in the control group vs 20.7 (0.31) in the colchicine group (log rank P = .03). Adverse events were similar in the 2 groups, except for diarrhea, which was more frequent with colchicine group than the control group (25 patients [45.5%] vs 9 patients [18.0%]; P = .003).



Kaplan-Meier Curves for Survival from the Primary Clinical End Point

CONCLUSIONS

In this analysis, in contrast with a control group, patients who obtained colchicine had statistically important increased duration for clinical worsening. The observed discrepancy, however, was focused on a small margin of clinical significance; hence such findings should be viewed as producing hypothesis. There were no differences between the groups in levels of hs cTn or C-reactive proteins.

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Restricted versus liberal intraoperative benzodiazepine use in cardiac anesthesia to reduce delirium

INTRODUCTION

Delirium impacts 15 to 25 percent of adults following cardiac operation and is correlated with extended duration of stay (LOS), readmission to hospital, long-term cognitive and physical impairment. Observational studies have suggested an association between perioperative administration of benzodiazepine and delirium in both cardiac and non-cardiac surgical populations and in mechanically ventilated ICU patients. A recent meta-analysis of RCTs comparing BZD to dexmedetomidine for ICU sedation has shown a trend towards increased delirium with benzodiazepine sedation, with a relative risk (RR) of 1.23. Though not statistically relevant, the Society of Critical Care Medicine (SCCM) has found this finding to be underpowered and scientifically essential enough to influence recommendations in the guidelines. Consequently, the SCCM and American Geriatrics Society guidelines advocate limiting the usage of benzodiazepines in chronically sick and elderly adult communities. However, intraoperative benzodiazepine administration during cardiac surgery remains common due to their favorable haemodynamic profile and amnestic properties that are thought to prevent intraoperative consciousness.

No RCT evidence relating to the effects of intraoperative administration of benzodiazepine is available. Throughout existing experience in cardiac anaesthesia, there are two common strategies to intraoperative benzodiazepine administration: one that seldom contains benzodiazepines and one that occasionally does not contain benzodiazepines. A research is required to determine how generally adopting a cardiac anaesthesia strategy that seldom involves intraoperative benzodiazepines decreases the occurrence of postoperative delirium in adults following cardiac surgery. Cardiac surgery is conducted in specialist high-volume hospitals to eliminate risks and improve performance and is focused primarily on the usage of clinical systematic protocols, such as pre-operative evaluation and pre- and post-operative treatment processes.

Since cardiac treatment is structured by traditional institutional policy, these policies may promote the estimation of the effect of constrained vs. radical intraoperative BZD use. Checking the results of various interventions often encourages a proactive nature of experiments, with systemic rather than individual randomisation, such that the procedure is evaluated in the context in which it may be applied. Authors have therefore designed a realistic randomized cluster hybrid experiment to check how an operational approach of controlled usage of benzodiazepines during surgery (compared to unrestricted usage) decreases postoperative delirium. They've done a pilot test to determine the viability of this project. Author’s feasibility objectives included assessing the degree of physician adherence to each institutional policy to which the hospital was randomised, and then to the alternate policy to which the hospital crossed over. They also wanted to determine whether delirium measurement can be achieved using data gathered as part of routine clinical care. The ultimate aim was to assess the frequency of intraoperative sensitivity within the short amounts of benzodiazepine.

METHODS

They conducted a two-centre, pilot, randomised cluster crossover trial with four 4-week crossover periods. Each centre was randomised to a policy of restricted or liberal use, and then alternated between the two policies during the remaining three periods. Author's feasibility outcomes were adherence to each policy and outcome assessment. They also evaluated the incidence of intraoperative awareness in one site using serial Brice questionnaires.

RESULTS

Of 800 patients undergoing cardiac surgery during the trial period, 127/800 (15.9%) had delirium. Of these, 355/ 389 (91.3%) received benzodiazepines during the liberal benzodiazepine periods and 363/411 (88.3%) did not receive benzodiazepines during the restricted benzodiazepine periods. Amongst the 800 patients, 740 (92.5%) had ≥1 postoperative delirium assessment per day in the ICU. Of 521 patients screened for intraoperative awareness, one patient (0.2%), managed during the restricted benzodiazepine period (but who received benzodiazepine), experienced intraoperative awareness.

	Restricted benzodiazepine use (*n*=411)	Liberal benzodiazepine use (*n*=389)	P-value
Feasibility outcomes			
Proportion of patients managed according to policy, *n* (%)	363 (88.3)	355 (91.3)	0.171
Proportion of patients with at least one delirium scale assessment in the cardiovascular ICU, *n* (%)	398 (96.87)	372 (95.6)	0.369
Proportion of patients with at least one delirium scale assessment per day in the cardiovascular ICU, *n* (%)	382 (92.93)	358 (92.0)	0.624
Incidence of intraoperative awareness, *n* (%)	1 (0.4%)* (*n*=263)	0 (0) (*n*=258)	1.00†
Outcomes of main trial			
Delirium, *n* (%)	72 (17.5)	55 (14.1)	0.191
ICU LOS (h), median (IQR)	24 (24–48)	24 (24–72)	0.148‡
Hospital LOS (days), median (IQR)	7 (5–11)	7 (5–11)	0.393‡
In-hospital mortality, *n* (%)	5 (1.2)	4 (1.0)	0.801

Feasibility outcomes and clinical outcomes of main B-Free trial by intervention arm. CVICU, cardiovascular ICU; IQR, interquartile range; LOS, length of stay. *Managed during limited benzodiazepine period, but received benzodiazepine. yFisher's exact test was used. zWilcoxon rank-sum test was used.

CONCLUSIONS

Delirium appears to arise following heart surgery in 15 to 20 per cent of ICU cases. It is correlated with substantial morbidity and mortality which could be due to the ongoing usage during operation of benzodiazepines. There are alternatives to benzodiazepines, although there is also confusion as to whether or not benzodiazepines can be used during surgery, as shown by the wide difference in clinical practice across Canada. In practice this heterogeneity represents a lack of evidence. A trial is required to decide the optimal approach to the administration of benzodiazepine (restricted vs liberal) during cardiac surgery.

In the B-Free pilot study, they have shown the viability of a hybrid experiment with multicenter clusters tackling this critical problem. They have seen that they can get universal conformity to both.

Intervention arm strategies, gather key results of the main study use only delirium tests conducted as part of standard clinical treatment, so ensure a restricted intraoperative response to benzodiazepine is not correlated with an elevated likelihood of intraoperative knowledge.

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