Selepressin for Patients With Septic Shock

To the Editor Compared with placebo, the nonadrenergic vasopressor angiotensin II was shown to increase mean arterial pressure after 3 hours in patients with vasodilatory shock in the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial (primary end point).[1] In addition, angiotensin II also reached the secondary goal of a greater reduction in the cardiovascular Sequential Organ Failure Assessment (SOFA) score after 48 hours vs placebo. As a consequence, research with angiotensin II continued and it was approved by the US Food and Drug Administration.

In the Selepressin Evaluation Program for Sepsis-Induced Shock–Adaptive Clinical Trial (SEPSIS-ACT), the nonadrenergic vasopressor selepressin, compared with placebo, did not result in improvement in the primary outcome (ventilator- and vasopressor-free days) or in any of the secondary end points (90-day mortality, kidney replacement therapy–free days, intensive care unit–free days) in patients with septic shock.[2] Thus, the first question: Is selepressin a less effective nonadrenergic vasopressor than angiotensin II? No answer can be provided based on 2 different studies evaluating only 1 of the compounds. Nevertheless, the differences in attainment of the respective primary and secondary end points are suggestive.

The second question is: Did the authors of the SEPSIS-ACT trial choose the wrong end points? Selepressin treatment not only resulted in an increased mean arterial pressure for up to 6 hours, it also decreased norepinephrine requirements and reduced cardiovascular SOFA scores at 24 and 48 hours compared with placebo. In addition, in agreement with preclinical studies,[3,4] urine output was increased and positive fluid balance reduced after 24 hours. Considering the importance of kidney dysfunction and fluid accumulation in patients with septic shock, these results may be relevant.

The final question is: What is the destiny of selepressin? Research with selepressin ended after SEPSIS-ACT stopped recruiting. We hope that the authors point out the numerous positive effects of selepressin that deserve further investigation before another promising drug for septic shock therapy is discarded.

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In Reply We agree with Dr Rehberg and colleagues that our study demonstrated that selepressin had a number of advantageous physiologic effects on blood pressure, urine output, and other features associated with septic shock.[1] In this way, as the authors suggest, it appears that selepressin shares a set of properties similar to that of other agents used for cardiovascular support in septic shock, including the recently approved angiotensin II.[2] In contrast to the study on which angiotensin II was approved, we chose a primary outcome designed to determine whether care with selepressin improved downstream patient-centered outcomes, and, at least in this setting, we were unable to demonstrate any such improvement. That said, we were reassured that there was no obvious sign that care with selepressin was associated with more adverse events than care with norepinephrine alone. Rehberg and colleagues note there are limited data suggesting that any vasopressor improves downstream patient-centered outcomes compared with any other and therefore imply that if selepressin appears to work as well as other vasopressors, surely it should be added to the armamentarium of vasopressors for the care of septic shock, or at least be available for further evaluation. This line of reasoning represents one side of an old argument, namely, is there value in providing clinicians with a larger number of agents with clinically similar effects? Rehberg and colleagues, at least in this instance, seem to think so, and either way, we agree this is an important question to consider.

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Conflict of Interest Disclosures: Dr Angus reported receiving personal fees from Ferring Pharmaceuticals, Bristol-Myers Squibb, Bayer AG, and Beckman Coulter Inc and that he is a stockholder in Alung Technologies. In addition, Dr Angus has patents or patents pending for selepressin (compounds, compositions, and methods for treating sepsis) and proteomic biomarkers of sepsis in elderly patients. Dr Laterre reported receiving a grant from Ferring Pharmaceuticals, receiving personal fees from St Luc Hospital and the St Luc University Clinical Coordinating Center, formerly being a consultant at Ferring, and being a consultant at Adrenomed. Dr Lewis reported being the senior medical scientist at Berry Consultants LLC, the statistical consulting firm that designed the SEPSIS-ACT clinical trial.

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Risk of Offspring Birth Defects in Women After Bariatric Surgery

To the Editor In a Research Letter, Dr Neovius and colleagues investigated the association between gastric bypass surgery and risk of birth defects in offspring.[1] The authors found that bariatric surgery was protective against birth defects.

Although the data set was large, the results are somewhat challenging to interpret because of the choice of comparison group. The authors identified 2921 pregnant women with previous gastric bypass surgery and a comparison group of pregnant women with no history of bypass surgery. Women were matched on several risk factors for birth defects, including weight and diabetes. However, the authors matched the presurgery body mass index (BMI) for exposed women with the BMI at the time of pregnancy for controls. Similarly, women who had diabetes before surgery were matched with controls who had diabetes during pregnancy. Because women were less obese and had better glucose control after gastric bypass surgery, the authors compared women who lost weight after surgery with women who were more obese and had diabetes. Obesity and diabetes are both risk factors for birth defects;[2] thus, it is expected that women who lose weight after bariatric surgery will have a lower risk of birth defects. The results confirm that weight loss is an effective tool to reduce the risk of birth defects but do not answer the question of whether women with gastric bypass procedures have an elevated risk of birth defects relative to women with similar weight.

This issue is important because Roux-en-Y gastric bypass surgery may lead to intestinal malabsorption,[3] which is associated with nutrient deficiencies that increase the risk of birth defects.[4] Folic acid deficiency in particular is an established risk factor for birth defects.[4] In a Canadian study, women with previous bariatric surgery had 1.20 times the risk of birth defects compared with nonobese women who did not have surgery.[5] Moreover, the associations disappeared after folic acid food fortification, suggesting that nutrient deficiencies may be prevalent in pregnant women with a history of bariatric surgery.[5]

Without comparing women who underwent gastric bypass surgery with women of similar weight at the time of pregnancy, it is difficult to be certain that bariatric surgery is not a risk factor for birth defects.

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In Reply We agree with Dr Auger and colleagues that there are several effects of gastric bypass surgery that may influence the risk of birth defects, including positive effects from weight loss and improved glucose control, as well as negative effects such as nutrient deficiencies and increased risk of substance abuse.[1]

With our study design, matching controls and gastric bypass surgery–exposed women on presurgery data regarding BMI, diabetes, and substance abuse, we attempted to answer the research question of whether gastric bypass surgery (vs no surgery) influences the risk of offspring birth defects.[2] It aimed to inform women with severe obesity, prior to surgical intervention, about the risk or benefit for postsurgery pregnancy and childbirth. Hence, we estimated the net effect from both positive and negative consequences of treatment.

Auger and colleagues suggest that early-pregnancy body weight, rather than presurgery data, should be used as a matching factor. We did not design our study that way, as early-pregnancy body weight is downstream of the surgical intervention and on the causal pathway between the intervention (gastric bypass surgery) and the outcome (birth defects).[3] In an attempt to estimate the effect of gastric bypass surgery vs no such surgery on the risk of offspring birth defects, matching for factors on the causal pathway (such as postsurgery body weight, BMI, diabetes, or substance abuse) would introduce bias.

The alternative design suggested by Auger and colleagues, matching for postintervention body weight, would answer a different research question, namely whether 2 pregnant women, discordant on gastric bypass surgery status but with similar body weight in early pregnancy, have different risks of offspring birth defects. The answer to that question may be of interest to midwives and obstetricians when deciding on type and intensity of monitoring during pregnancy in women with a history of gastric bypass surgery. However, it does not inform women with severe obesity who may be contemplating bariatric surgery about the net risk or benefit of having surgery before vs after pregnancy and childbirth.

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