

VIEWPOINT

Does intensive insulin therapy really reduce mortality in critically ill surgical patients? A reanalysis of meta-analytic data

Jan O Friedrich^{1,2,3*}, Clarence Chant⁴ and Neill KJ Adhikari^{1,5}

Abstract

Two recent systematic reviews evaluating intensive insulin therapy (IIT) in critically ill patients grouped randomized controlled trials (RCTs) by type of intensive care unit (ICU). The more recent review found that IIT reduced mortality in patients admitted to a surgical ICU, but not in those admitted to medical ICUs or mixed medical–surgical ICUs, or in all patients combined. Our objective was to determine whether IIT saves lives in critically ill surgical patients regardless of the type of ICU. Pooling mortality data from surgical and medical subgroups in mixed-ICU RCTs (16 trials) with RCTs conducted exclusively in surgical ICUs (five trials) and in medical ICUs (five trials), respectively, showed no effect of IIT in the subgroups of surgical patients (risk ratio = 0.85, 95% confidence interval (CI) = 0.69 to 1.04, $P = 0.11$; $I^2 = 51\%$, 95% CI = 1 to 75%) or of medical patients (risk ratio = 1.02, 95% CI = 0.95 to 1.09, $P = 0.61$; $I^2 = 0\%$, 95% CI = 0 to 41%). There was no differential effect between subgroups (interaction $P = 0.10$). There was statistical heterogeneity in the surgical subgroup, with some trials demonstrating significant benefit and others demonstrating significant harm, but no surgical subgroup consistently benefited from IIT. Such a reanalysis suggests that IIT does not reduce mortality in critically ill surgical patients or medical patients. Further insights may come from individual patient data meta-analyses or from future large multicenter RCTs in more narrowly defined subgroups of surgical patients.

Introduction

Two recent systematic reviews that evaluated intensive insulin therapy (IIT) in critically ill patients grouped the included randomized controlled trials (RCTs) by type of intensive care unit (ICU): surgical versus medical versus mixed medical–surgical [1,2]. Both reviews found no mortality reduction among all critically ill patients. The more recent review by Griesdale and colleagues, however, found that IIT reduced mortality in patients admitted to surgical ICUs, but not in patients admitted to medical ICUs or mixed medical–surgical ICUs [2]. Potential explanations to support the beneficial effects of IIT among critically ill surgical patients were proposed in the accompanying editorial: a greater use of central and arterial lines in surgical ICUs, which allows for more accurate monitoring and correction of blood glucose; acute hyperglycemia in surgical patients, who are more likely to benefit from correction than medical patients with chronic elevations and adaptive responses; and better achievement of target glucose levels in surgical ICU studies compared with medical ICU or mixed ICU studies [3]. In contrast to the finding of the most recent review, however, the large NICE-SUGAR RCT enrolling over 6,000 critically ill patients suggested increased mortality both overall and among the subgroup of surgical patients [4]. (This largest trial to date was included in the most recent review but was analyzed among the mixed medical–surgical ICU group of trials [2].)

These contrasting results between the meta-analyses [1,2] and the most recent trial [4] may stem from sensitivity of the meta-analytic results to methodologic decisions. In particular, the decision to group trials by type of ICU rather than by type of patient may not be intuitive for clinicians, for whom the important question is whether IIT saves lives in critically ill surgical patients regardless of the type of ICU in which they are treated, which depends on hospital organization. The objective of the present viewpoint article was therefore to determine whether IIT has a differential effect in surgical compared with medical critically ill patients by incorporating all available

*Correspondence: j.friedrich@utoronto.ca

²Critical Care and Medicine Departments, St Michael's Hospital, 30 Bond Street, Bond Wing, Room 4-015 Bond, Toronto, Ontario, Canada M5B 1W8
Full list of author information is available at the end of the article

outcomes data from surgical and medical subgroups in mixed ICU trials.

Categorizing surgical and medical subgroups by type of patient rather than type of ICU

We considered all trials of IIT included in the two recent systematic reviews [1,2]. Our primary analysis used the RCTs included in the more recent review [2], which found differential effects between patients admitted to medical ICUs and surgical ICUs. The review's primary outcome was 90-day mortality – or, if not available, then hospital mortality, 28-day mortality, or ICU mortality (in descending order of preference; two trials reported only 6-month mortality). Since both reviews were published recently, we did not update the literature search; for included conference abstracts, however, we searched for and used data from subsequently published full reports. For trials conducted in mixed ICUs, we extracted mortality data separately for surgical and medical subgroups, and contacted authors to request subgroup data when not reported in the original publication. We grouped these outcomes with data reported in trials conducted exclusively in surgical ICUs and in medical ICUs. We used the categorization of surgical patients and medical patients by the authors of the mixed ICU RCTs and assumed that trials conducted in surgical ICUs and medical ICUs included exclusively surgical patients and medical patients, respectively. For one RCT, classified differently in the two systematic reviews [1,2], we confirmed with the study authors that the trial was conducted in a mixed ICU [5]. For our primary analysis, we constructed a surgical subgroup including trial-level data from the surgical ICU trials and surgical group-level data from the mixed ICU trials. We used a similar approach for the medical subgroup.

Mortality data in each subgroup were pooled using random-effects models, which incorporate between-study heterogeneity (Review Manager; Cochrane Collaboration, Oxford, UK), expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Pooled RRs in the surgical and medical subgroups were compared using a *z* test, with a significance level of 0.05. Statistical between-trial heterogeneity within each subgroup was assessed using the *I*² measure with 95% CIs [6].

We conducted three sensitivity analyses. The first included only trials conducted in mixed ICUs that enrolled both surgical patients and medical patients. This analysis addresses the possibility that differences between trials other than patient population could explain differential effects. The second analysis included trials in the first systematic review by Wiener and colleagues [1] that were excluded by the more recent review by Griesdale and colleagues [2]. The third analysis included only trials that actually achieved tight glucose control, as defined by a

mean blood glucose of 4.4 to 6.1 mM (the most commonly targeted range) in the intervention group.

Of the 16 RCTs conducted in mixed ICUs [4,5,7-20], mortality data for surgical and medical subgroups were available for 14 RCTs [4,5,7-18] and were unavailable for one RCT [19] after author contact; we were unable to contact the authors of one study [20]. These 14 RCTs provided data for 9,935/10,206 (97%) of patients randomized in mixed ICU trials [4,5,7-18]. These data were combined with the five RCTs (1,972 patients) conducted exclusively in surgical ICUs [21-25] and the five RCTs (1,371 patients) in medical ICUs [26-30] included in the most recent review. For each included trial, Table 1 presents the target and mean achieved blood glucose values for both treatment groups and the mortality time point analyzed.

Meta-analyses showed no effect of IIT in the subgroups of surgical patients (RR = 0.85, 95% CI = 0.69 to 1.04, *P* = 0.11) or of medical patients (RR = 1.02, 95% CI = 0.95 to 1.09, *P* = 0.61) (Figure 1 and Table 2). There was no evidence of a differential effect between subgroups (*P* = 0.10). There was moderate statistical heterogeneity in the surgical subgroup (*I*² = 51%, 95% CI = 1 to 75%) but none in the medical subgroup (*I*² = 0%, 95% CI = 0 to 41%). Considering surgical patients, the effect of IIT appeared consistent in the subgroup of surgical ICU trials, in which the point estimate for *I*² is 0%. However, the 95% confidence interval of this estimate of heterogeneity (0 to 70%) is wide and similar to the *I*² confidence interval for both the surgical subgroup of the mixed ICU studies and the entire surgical patient population (see Figure 1a). This suggests that substantial heterogeneity cannot be excluded [31], even in the subgroup of surgical ICU trials.

Results of sensitivity analyses were similar to those of the primary analysis (Table 2). First, the analysis restricted to 12 mixed ICU trials enrolling both surgical and medical patients found RR = 0.98 (95% CI = 0.80 to 1.19, *P* = 0.82; *I*² = 40%) in surgical patients and RR = 1.03 (95% CI = 0.94 to 1.13, *P* = 0.51; *I*² = 8%) in medical patients (*P* = 0.66 for comparison of RRs). Second, the analysis adding the results of the three surgical ICU trials [32-34] and the three medical ICU trials [35-37] included only in the earlier systematic review [1] found RR = 0.89 (95% CI = 0.74 to 1.08, *P* = 0.24; *I*² = 45%) in surgical patients and RR = 1.02 (95% CI = 0.96 to 1.09, *P* = 0.46; *I*² = 0%) in medical patients (*P* = 0.18 for comparison of RRs). Finally, the analysis of trials achieving tight glucose control (four out of eight surgical ICU trials, two out of eight medical ICU trials, and five out of 14 mixed ICU trials) found RR = 0.76 (95% CI = 0.57 to 1.01, *P* = 0.06; *I*² = 10%) in surgical patients and RR = 1.04 (95% CI = 0.71 to 1.53, *P* = 0.82; *I*² = 7%) in medical patients (*P* = 0.20 for comparison of RRs). This last subgroup

Table 1. Target and achieved blood glucose and mortality outcome time point by trial

Study	Intervention group		Control group		Mortality outcome time point
	Glucose target (mM)	Mean achieved glucose (mM)	Glucose target (mM)	Mean achieved glucose (mM)	
Studies included in the more recent systematic review [2]					
Surgical ICU studies					
Van den Berghe and colleagues [21]	4.4 to 6.1	5.7	10.0 to 11.1	8.5	Hospital
Grey and Perdrizet [22]	4.4 to 6.7	6.9	10.0 to 12.2	9.9	Hospital
Bilotta and colleagues (SAH) [23]	4.4 to 6.7	5.0	<12.2	8.3	6-month
He and colleagues [24]	4.4 to 8.3	6.7	10.0 to 11.1	10.0	Hospital
Bilotta and colleagues (TBI) [25]	4.4 to 6.7	5.1	<12.2	8.2	6-month
Medical ICU studies					
Bland and colleagues [26]	4.4 to 6.1	5.8	10.0 to 11.1	9.8	28-day
Van den Berghe and colleagues [27]	4.4 to 6.1	6.2	10.0 to 11.1	8.5	90-day
Walters and colleagues [28]	5.0 to 8.0	6.9	≤15.0	8.1	30-day
Oksanen and colleagues [29]	4.0 to 6.0	5.0	6.0 to 8.0	6.4	30-day
Bruno and colleagues [30]	5.0 to 7.2	7.4	<11.1	10.6	90-day
Mixed medical–surgical ICU studies					
Mitchell and colleagues [8]	4.4 to 6.1	5.4	10.0 to 11.1	7.9	Hospital
Azevedo and colleagues [9]	4.4 to 6.7	7.4	<10.0	8.0	ICU
Preiser and colleagues [11]	4.4 to 6.1	6.6	7.8 to 10.0	8.2	Hospital
Brunkhorst and colleagues [12]	4.4 to 6.1	6.2	10.0 to 11.1	8.4	90-day
lapichino and colleagues [13]	4.4 to 6.1	6.1	10.0 to 11.1	9.1	90-day
He and colleagues [14]	4.4 to 6.1	5.1	10.0 to 11.1	10.6	ICU
Zhang and colleagues [15]	4.4 to 6.1	6.1	10.0 to 11.1	7.7	Hospital
De La Rosa and colleagues [16]	4.4 to 6.1	6.5	10.0 to 11.1	8.2	Hospital
Arabi and colleagues [17]	4.4 to 6.1	6.4	10.0 to 11.1	9.5	Hospital
Mackenzie and colleagues [18]	4.0 to 6.0	7.0	<11.0	8.4	Hospital
NICE-SUGAR [4]	4.5 to 6.0	6.4	<10.0	8.0	90-day
Farah and colleagues [5]	6.1 to 7.8	7.9	7.8 to 11.1	9.7	28-day
Yu and colleagues [7]	4.4 to 6.1	5.7	10.0 to 11.1	11.1	Hospital
McMullin and colleagues [10]	5.0 to 7.0	7.1	8.0 to 10.0	9.4	Hospital
Additional studies included only in the earlier systematic review [1]					
Surgical ICU studies					
Stecher and colleagues [32]	4.4 to 6.1	n/a	7.8 to 10.0	n/a	n/a
Kia and colleagues [33]	4.2 to 6.4	6.0	10.0 to 11.1	8.0	90-day
Chan and colleagues [34]	4.4 to 6.7	7.0	<11.1	9.3	Hospital
Medical ICU studies					
Fernandez and colleagues [35]	4.4 to 6.1	6.7	<8.3	11.4	Hospital
Davies and colleagues [36]	4.0 to 8.0	10.3	<10.0	10.7	Hospital
Gray and colleagues [37]	4.0 to 7.0	6.3	<17.0	6.8	90-day

ICU, intensive care unit; n/a, not available; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

analysis is dominated by the largest surgical ICU trial [21] and excludes the six other largest trials (one in a medical ICU [27] and five in mixed ICUs [4,11,12,16,17]) that targeted the same blood glucose range in the intervention group (4.4 to 6.1 mM) but achieved slightly higher mean values (6.2 to 6.6 mM). Although there was

a nonsignificant trend to benefit of IIT in the surgical subgroup considered in isolation for this sensitivity analysis, there is no evidence that the effect differed from medical patients.

Given this lack of difference between surgical and medical subgroups in any of the primary or secondary

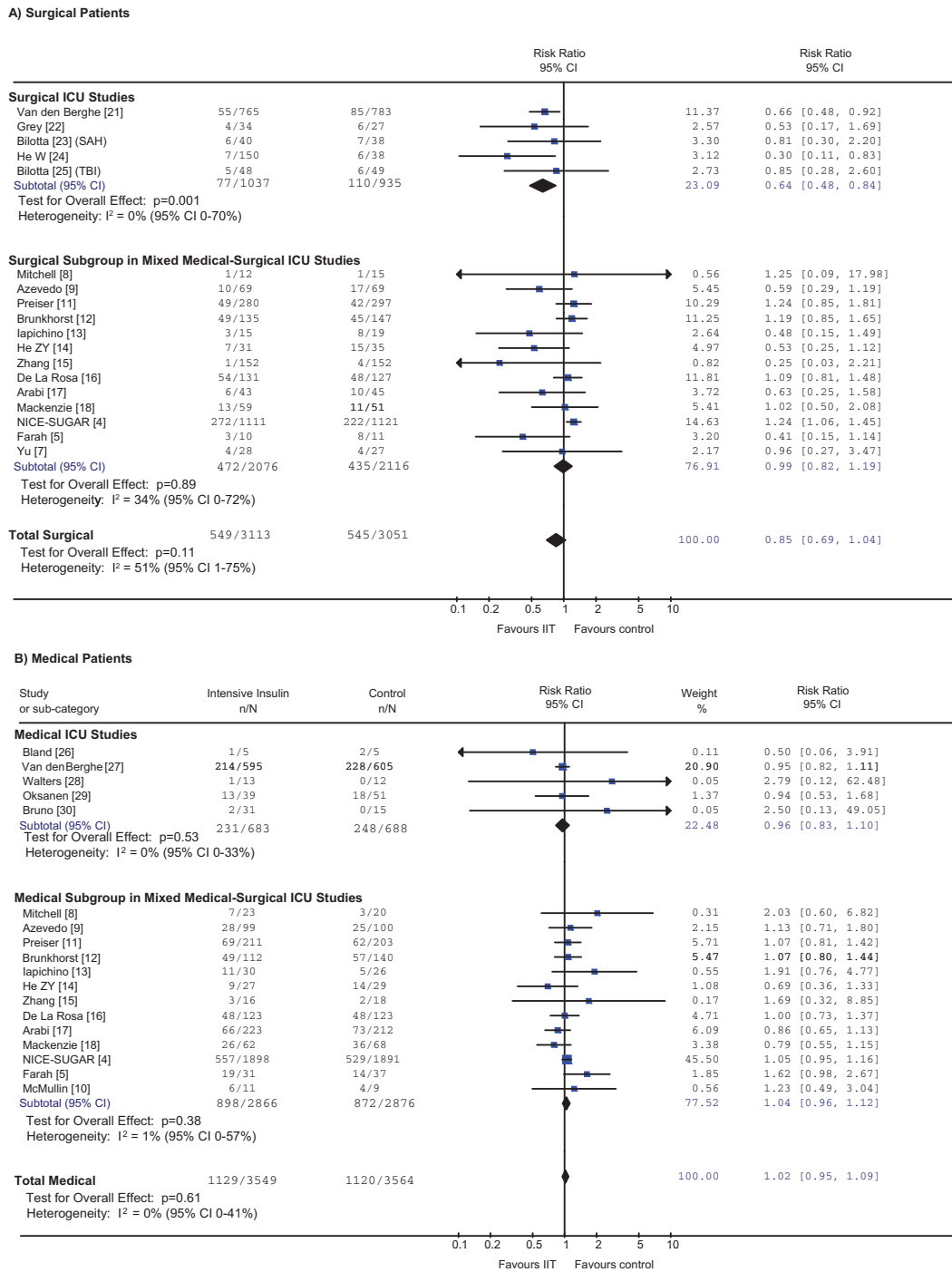


Figure 1. Effect of intensive insulin therapy on mortality in surgical and medical patients. A z test of interaction between the risk ratio (RR) for mortality in (A) all surgical patients and (B) all medical patients was not statistically significant ($P = 0.10$), indicating that treatment effects did not differ between these two groups. This was also the case if one compares medical and surgical patients only within the same – that is, mixed intensive care unit (ICU) – trials ($P = 0.66$). Of the 14 trials conducted in mixed ICUs [4,5,7-18], one enrolled only surgical patients [7] and one enrolled only medical patients [10]. Preiser and colleagues' article [11] is the full publication of the abstract included in the most recent review [2]. After accounting for readmissions, subgroup-specific outcomes data were available for 991 out of 1,078 patients randomized. Compared with data presented in the most recent systematic review [2], subgroup-specific outcomes data are complete for all other trials except for 1/535 patients with missing data in one trial [12]. CI, confidence interval; I^2 , percentage of total variation across studies due to between-study heterogeneity rather than chance; IIT, intensive insulin therapy; n/N = number of deaths/number of patients randomized; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

Table 2. Summary of pooled results of primary and sensitivity analyses

Analysis	Pooled results			P value ^b
	All trials ^a	Surgical patient subgroup	Medical patient subgroup	
Primary				
Trials included in more recent review [2] ^c	0.93 (0.84 to 1.04, <i>P</i> = 0.20), <i>I</i> ² = 45% (2 to 69%); 26 trials; 13,549 patients	0.85 (0.69 to 1.04, <i>P</i> = 0.11), <i>I</i> ² = 51% (1 to 75%); 18 trials; 6,164 patients	1.02 (0.95 to 1.09, <i>P</i> = 0.61), <i>I</i> ² = 0% (0 to 41%); 18 trials; 7,113 patients	0.10
Sensitivity				
Only mixed ICU trials enrolling both surgical and medical patients	0.97 (0.85 to 1.11, <i>P</i> = 0.66), <i>I</i> ² = 54% (0 to 79%); 14 trials; 10,121 patients	0.98 (0.80 to 1.19, <i>P</i> = 0.82), <i>I</i> ² = 40% (0 to 75%); 12 trials; 4,137 patients	1.03 (0.94 to 1.13, <i>P</i> = 0.51), <i>I</i> ² = 8% (0 to 62%); 12 trials; 5,722 patients	0.66
Incorporating additional trials included in earlier review [1]	0.96 (0.87 to 1.06, <i>P</i> = 0.43), <i>I</i> ² = 36% (0 to 61%); 32 trials; 15,051 patients	0.89 (0.74 to 1.08, <i>P</i> = 0.24), <i>I</i> ² = 45% (0 to 71%); 21 trials; 6,644 patients	1.02 (0.96 to 1.09, <i>P</i> = 0.46), <i>I</i> ² = 0% (0 to 31%); 21 trials; 8,135 patients	0.18
Only trials achieving mean blood glucose 4.4 to 6.1 mM in IIT group	0.80 (0.60 to 1.07, <i>P</i> = 0.14), <i>I</i> ² = 43% (0 to 76%); 12 trials; 2,879 patients	0.76 (0.57 to 1.01, <i>P</i> = 0.06), <i>I</i> ² = 10% (0 to 68%); 9 trials; 2,474 patients	1.04 (0.71 to 1.53, <i>P</i> = 0.82), <i>I</i> ² = 7% (0 to 76%); 6 trials; 289 patients	0.20

Data presented as risk ratio (95% confidence interval). *P*, percentage of total variation across studies due to between-study heterogeneity rather than chance; ICU, intensive care unit; IIT, intensive insulin therapy. ^aIncludes also mixed ICU trials for which separate surgical and medical subgroup data were not available [19,20]. ^bSurgical versus medical interaction. ^cSee also Figure 1.

analyses, the best estimate of IIT effect in both subgroups is the overall effect, which is nil (see Table 2).

Discussion and conclusions

Our analysis shows no effect of IIT in surgical or medical critically ill patients. We found moderate between-trial differences in the effect of IIT in the surgical subgroup, reflecting the contrasting results of two trials enrolling the most surgical patients: the study by Van den Berghe and colleagues [21] and the NICE-SUGAR study [4]. As noted by other studies [1,2,21,38,39], multiple factors may have contributed to the positive result in the single-center trial by Van den Berghe and colleagues that mainly enrolled cardiac surgery patients [21]: patient population (higher control group mortality than expected), local care practices (in particular, routine use of intravenous glucose and parenteral nutrition [40]), early stopping after an interim analysis showed benefit, and a higher target glucose range in the control group compared with other trials.

Furthermore, our analysis reveals the variable definitions of surgical patients that may also have contributed to between-trial heterogeneity: some trials included only postoperative patients, while others also included patients who required ICU readmission from surgical wards or nonoperative patients with surgical diagnoses such as pancreatitis or trauma. Based on the available data, there does not appear to be any obvious subgroup of surgical patients that consistently benefits from IIT. Of the two trials conducted in patients after cardiac surgery, Van den Berghe and colleagues found a mortality benefit [21], but the much smaller trial by Chan and colleagues did not [34]. Moreover, Van den Berghe and colleagues' trial included patients who required ICU

readmission from surgical wards in addition to immediately postoperative patients. Other trials classified such patients as medical, and no trial suggested benefit in medical patients. Furthermore, in the NICE-SUGAR trial, operative patients were defined as immediately postoperative ICU admissions – and this trial actually suggested harm in such patients [4].

In summary, we analyzed the effect of IIT in surgical patients, regardless of the type of ICU to which they were admitted, and found no effect on mortality – similar to the effect for critically ill medical patients and all critically ill patients combined [1,2]. We therefore do not recommend this intervention for critically ill surgical patients or critically ill medical patients. Further insights into the effects of this intervention in surgical patients may come from individual patient data meta-analyses, acknowledging the challenges of ensuring availability and comparability of data among trials and obtaining expert statistical support. Alternatively, future large multicenter RCTs in specific patient subgroups, such as cardiac surgical patients, may further refine our understanding of the role of IIT in the ICU.

Abbreviations

CI, confidence interval; *P*, percentage of total variation across studies due to between-study heterogeneity rather than chance; ICU, intensive care unit; IIT, intensive insulin therapy; RCT, randomized controlled trial; RR, risk ratio.

Competing interests

The authors declare that they have no competing interests.

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Author details

¹Interdepartmental Division of Critical Care and Department of Medicine, University of Toronto, R. Fraser Elliot Building, 3rd Floor, South Wing, 3S-805, 190 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4. ²Critical Care and Medicine Departments, St Michael's Hospital, 30 Bond Street, Bond Wing, Room 4-015 Bond, Toronto, Ontario, Canada M5B 1W8. ³Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8. ⁴Department of Pharmacy, St Michael's Hospital, 30 Bond Street, Queen Wing, Room Q4036, Toronto, Ontario, Canada M5B 1W8. ⁵Department of Critical Care Medicine and Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5.

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