Dexmedetomidine versus propofol or midazolam in patients with abdominal sepsis regarding inflammatory response and capillary leak

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ABSTRACT

Background: Abdominal sepsis patients suffer from profound intravascular fluid deficit due to concomitant inflammatory response and capillary leakage. It is reported that anti-inflammatory properties of sedative agents can control inflammatory cascade in many experimental septic conditions. We aimed to investigate the best sedative drug for inflammatory responses and capillary leak in patients with abdominal sepsis.

Methods: In this prospective randomized study, 60 patients with abdominal sepsis who underwent abdominal surgery and required post-operative sedation and mechanical ventilation were randomized into 3 groups in a 1:1:1 ratio. Group D (sedated with dexmedetomidine), group P (sedated with propofol), and group M (sedated with midazolam). This study was held in intensive care units of Assiut University Hospitals with primary outcome was serum IL-6 and IL-1β. Secondary outcomes were capillary leak index, lactate clearance, vasopressor requirements, total intake, total output, and fluid balance.

Results: Dexmedetomidine significantly reduced levels of IL-6 and IL-1β through 48 hours compared to both midazolam and propofol. Dexmedetomidine caused a significant decline in capillary leak index (p < 0.05) through 48 hours and significant higher lactate clearance (p = 0.03) in first 24 hours compared to both midazolam and propofol. Dexmedetomidine group had a significantly higher output, lower serum creatinine levels and lower positive fluid balance compared to propofol and midazolam.

Conclusions: Dexmedetomidine reduced inflammatory response and capillary leak in mechanically ventilated patients with abdominal sepsis with better lactate clearance and less fluid intake.

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1. Introduction

Sepsis is considered a life-threatening impairment of organs induced by a dysregulated host response to infection [1]. As an essential reason for non-trauma deaths and the second most pervasive reason for sepsis in critical cases, abdominal sepsis continues to be a significant problem in the resource-limited environment in developing countries, and its management represents a significant workload for most healthcare workers [2].

The inflammatory response associated with abdominal sepsis has grave consequences, including multiple organ dysfunction and death. White blood cells produce inflammatory mediators like interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α), as well as interferon-gamma (INF-γ) among critical cases. These mediators can damage endothelial cells, affecting capillary permeability and causing metabolic acidosis, hypotension, as well as multi-organ failure [3].

Volume overload is unavoidable during treatment of patients with abdominal sepsis as well as septic shock. This is attributed to the initial fluid resuscitation to restore intravascular volume, enhance cardiac output, and increase delivery of oxygen. In most septic conditions, the capillary leakage enhances the extravasation of massive quantities of fluid, resulting in a proportional central hypovolemia, which frequently necessitates more administration of fluid in spite of interstitial oedema. Capillary leak is fluid and electrolyte maladaptive loss with or without protein into the interstitial space, leading to generalized oedema and eventually organ dysfunction [4].

There is still no specific prevention or treatment for vascular leakage during sepsis. The immunomodulatory effects of sedative drugs have now been shown to induce a paradigm shift in the clinical course of pre-existing inflammatory processes, such as sepsis, acute respiratory distress syndrome, and delirium [5].

In search of the ideal sedative agent to be used in patients with abdominal sepsis, we aimed to investigate the optimal sedative to attenuate the inflammatory response by measuring IL-6 and IL-1β serum levels before and after sedation protocol. The secondary goals were capillary leak index of the studied patients and hemodynamic profile of the studied sedative drugs.

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2. Patients and methods

The current study is a prospective randomized blind study that was performed in the intensive care units of Assiut University Hospitals from January 2021 till April 2021. Patients were recruited after approval by the medical ethics committee of the Faculty of Medicine, Assiut University (IRB# 00008718). The study was registered at ClinicalTrials.gov (NCT04718714) and was adherent to the CONSORT guidelines (www.consort-statement.org). Written informed consent was obtained from the studied patients when possible or the next of kin.

The inclusion criteria were adult patients < 18 years old diagnosed with abdominal sepsis, who underwent urgent abdominal surgery to control the source of infection and required postoperative sedation and mechanical ventilation. Abdominal sepsis was determined as organ dysfunction with a substantial change in overall SOFA score [6] ≥ 2 points as a result of intra-abdominal infection. Exclusion criteria included known allergy to the studied drugs: propofol, dexmedetomidine, or midazolam, patient or legal guardian refusal, confirmed pregnancy and known or suspected brain death.

Permutated blocked randomization was done online (www.sealedenvelope.com) to generate the randomization list. Categorization of study group was reserved in closed non-transparent envelopes that were unsealed after patients’ enrolment. Participants or their guardians, the data collector, and the statistician were all blinded to the study assignment. The ICU clinicians and the bedside nurses were not blinded to the study assignment.

All patients received the same technique of general anaesthesia by rapid sequence induction with fentanyl 1 µg/kg, propofol 1 mg/kg, and rocuronium 1 mg/kg to intubate with cuffed endotracheal tube, then volume-controlled ventilation was used with appropriate settings to maintain normocarbia. A pre-induction arterial line for invasive blood pressure monitoring was inserted and a central venous line was inserted after induction. Patients were admitted to ICU postoperatively to be mechanically ventilated and to start the sedation protocol.

The patients were randomly classified into three groups. Group D (Dexmedetomidine), group P (Propofol), and group M (Midazolam) in a 1:1:1 ratio.

- **Group D:** Patients received dexmedetomidine (Precedex®; 200 µg/2 ml; Hospira, Inc., Lake Forest, USA) at one µg/kg loading dose over 10 minutes followed by a 0.2 – 1.5 µg/kg/hr. maintenance dose for 24 hours [7]. Dexmedetomidine was diluted in normal saline at a 4 µg/ml concentration.

- **Group P:** Patients were given propofol (Propofol 1%, Fresenius, Fresenius Kabi, Egypt) at one mg/kg loading dose over 15 minutes, after which they were given a 20–80 µg/kg/min maintenance dose for 24 hours [7]. Propofol was given without dilution, consequently each 1 ml contained 10 mg.

- **Group M:** Patients received midazolam (Dormicum®; 15 mg/3 ml, Roche Ltd, Basel, Switzerland) at a 0.2 mg/kg loading dose over 10 minutes, after which a maintenance dose of 0.02–0.2 mg/kg/hr. for 24 hours [8]. Midazolam was diluted in normal saline at a 1 mg/ml concentration.

The tested drug was infused intravenously through a 50 ml syringe and a dedicated intravenous line into a central or peripheral vein and no flushes were given through that line. The used syringe pump was Injectomat Agilia Fresenius Kabi, India. Subjects were maintained at a Ramsay sedation score [9] of 2 to 4 by adjusting the sedative dosage range.

3. ICU management

Monitoring of oxygen saturation, invasive mean arterial blood pressure (MAP), central venous pressure (CVP), heart rate, and temperature were done to all studied patients.

Patients were mechanically ventilated with appropriate ventilation settings that were adjusted to meet accepted values of blood gases. Extubation was performed when indicated clinically (alert and hemodynamically stabilized patients, who had normal serum electrolytes, arterial oxygen tension >74 mmHg over a concentration of inspired oxygen < 40%, and a positive end-expiratory pressure < 5 cmH₂O).

Patients who experienced sepsis-induced hypoperfusion, received adequate initial resuscitation with 30 ml/kg crystalloids guided by the surviving sepsis campaign bundle 2016 [10]. Resuscitation was guided to maintain MAP > 65 mmHg and to obtain lactate normalization in cases with elevated levels of lactate.

Vasopressors and inotropes were given to maintain MAP > 65 mmHg in patients in whom crystalloids fluids failed to achieve the target MAP. The vasopressors and the ranges of corresponding dose were norepinephrine (50 to 1000 ng/kg/min) and epinephrine (50 to 500 ng/kg/min).

Adequate postoperative analgesia, in the form of intravenous paracetamol (1 gm), was repeated twice, if it failed, I.V. nalbuphine (10 mg) was given according to a systematic pain assessment by behavioural pain scale.

Cultures were obtained before antibiotics. Broad-spectrum antibiotics with one or more intravenous antimicrobials were given empirically until the results of cultures and sensitivities were identified.
Cessation of sedation was done in the morning (as possible) for 2–4 hours for assessment of Glasgow comat scale and to assess weaning readiness (if the patient fulfilled weaning criteria, the sedation was stopped, if not, the sedation continued till end of study).

Serial arterial blood gas, bedside blood sugar measurements and daily laboratory investigations of CBC, INR, tests of renal and liver functions, and serum electrolytes were done on all study participants.

4. Data collection

Data collection and assessment parameters were obtained for 48 hours (since the start of infusion of studied drugs).

- Patients’ baseline characteristics (age, gender, and BMI), clinical data (diagnoses, operative time, and type of surgery) and patients’ baseline SOFA [6] and SAPS II scores [11] were collected 15 minutes before starting sedation.
- Invasive MAP (mmHg), heart rate (beat/minute), and CVP (cmH2O) were recorded every 120 min in the first 6 hours and every 6 hours until end of study.
- Daily and total intake (crystalloids, colloids, and blood products) and output (urine, nasogastric drainage, and surgical drains) and daily and total fluid balance for the first 48 hours of the admission to ICU were recorded.
- The dose of inotropes and vasopressors during the study period was calculated using norepinephrine equivalent dose (NEq) [12] in ng /kg/min.

\[(\text{NEq}) = \text{Norepinephrine dose in ng/kg/min} + \text{Epinephrine dose in ng/kg/min}.\]

- Serum lactate levels (mmol/L) were obtained at baseline, 24, and 48 hours.
- Capillary leak index (CLI) [13] was calculated at baseline, 24, and 48 hours and was equal to CRP (mg/dl)/serum Albumin (g/l) ratio multiplied by 100.
- Serum IL-6 and IL-1β levels (pg/ml) were measured at baseline, 24, and 48 hours.
- Serum creatinine (mg/dl) was measured at baseline, 24, and 48 hours.
- Incidence of adverse events for the studied drugs as bradycardia (heart rate decreased < 50 beats/minute) and hypotension (MAP < 60 mmHg). Bradycardia was treated with atropine 1 mg and hypotension was treated with a crystalloid bolus of 250 ml and increasing the inotropic/vasopressor infusion dose.

4.1. Sampling for cytokines

Five millilitres of venous blood were obtained in a plain tube. Centrifugation was done at 4000 rpm for 7 minutes to separate the serum. Samples were kept at −20°C until examination. Serum IL-6 as well as IL-1β level measurement was done by enzyme-linked immuno-sorbent assay (ELISA) using Cloud-Clone Corp ELISA kits. Before performing the assay, all samples were maintained at room temperature, and then mixed with gentle swirls. To avoid inter-assay variation, all sera were tested on the same day using the IMMULITE® 1000 immunoassay system (Siemens, Germany).

5. Outcome measurements

5.1. Primary outcome

Measurement of serum IL-6 at baseline, 24, and 48 hours.

5.2. Secondary outcomes

- Measurement of serum IL-1β at baseline, 24, and 48 hours.
- CLI at baseline, 24, and 48 hours.
- Vasopressor requirements at baseline, 24, and 48 hours as well as lactate clearance at 24 and 48 hours.
- Total intake, total output, and Fluid balance at first 24 hours, next 24 hours, and cumulative 48 hours.

6. Sample size

Sample size was determined guided by a prior study that used serum IL-6 concentration as the primary outcome [14]. By using G*Power 3.1.9.2 software program and with ANOVA Fixed effects test with α of 0.05, 80% power, and an effect size of 42%, the resulting sample size was 60 patients (20 in each group).

7. Statistical analysis

Statistical analysis was carried out utilizing IBM SPSS version 26 (USA). Patients’ outcomes were reported as categorical variables using percentages, or continuous variables using mean ± SD as well as median and range. With regard to continuous variables, Shapiro-Wilk test was employed as a test of normality. Comparisons between groups were performed using chi-square test for categorical variables, ANOVA test for normally distributed data and Kruskal-Wallis test for abnormally distributed data. P values less than 0.05 were considered statistically significant.
8. Results

8.1. Baseline characteristics

Two hundred twenty-two patients attending the general surgery department were screened for eligibility for our study. The causes of primary and secondary exclusion were illustrated in Figure 1. Finally, 60 patients were analysed, 20 in each treatment group. No significant differences had been detected between treatment groups regarding age, gender, BMI, and percentage of patients with associated medical disorders (P > 0.05). The causes of abdominal sepsis, the type, and duration of surgery and the baseline SOFA and SAPS II scores were comparable between the treatment groups (P > 0.05) (Table 1).

8.2. Inflammatory response

Dexmedetomidine significantly diminished IL-6 and IL-1β levels through the first 48 hours compared to both midazolam and propofol. Dexmedetomidine reduced IL-6 level to a lower value than propofol and midazolam

![Figure 1. CONSORT flow chart of the clinical trial.](image-url)
Table 1. Baseline characteristics.

| Variable                        | Midazolam | Propofol | Dexmedetomidine | P-value |
|---------------------------------|-----------|----------|-----------------|---------|
| Age (years, mean ± SD)          | 55.7 ± 9.6| 55.9 ± 7.7| 54 ± 8.2        | 0.67    |
| Gender                          | 0.8       |          |                 |         |
| Male (n, %)                     | 13 (65%)  | 11 (55%) | 12 (60%)        |         |
| Female (n, %)                   | 7 (35%)   | 9 (45%)  | 8 (40%)         |         |
| BMI (kg/m², mean ± SD)          | 28.6 ± 1.9| 28 ± 2   | 29.1 ± 1.7      | 0.14    |
| Operative time (minutes, mean ± SD) | 136.5 ± 20.4 | 134 ± 30.2 | 135 ± 29.6 | 0.9     |
| Percentage of associated medical diseases: | 0.054 |          |                 |         |
| - No medical disease (n, %)     | 0 (0%)    | 1 (5%)   | 5 (25%)         |         |
| - One medical disease (n, %)    | 18 (90%)  | 17 (85%) | 15 (75%)        |         |
| - Two or more medical diseases (n, %) | 2 (10%) | 2 (10%) | 0 (0%)          |         |
| Cause of abdominal sepsis       | 0.09      |          |                 |         |
| Perforated viscus (n, %)        | 6 (30%)   | 6 (30%)  | 5 (25%)         |         |
| Appendicular lesions (n, %)     | 1 (5%)    | 2 (10%)  | 1 (5%)          |         |
| Diverticulitis (n, %)           | 1 (5%)    | 1 (5%)   | 1 (5%)          |         |
| Anastomosis leakage (n, %)      | 2 (10%)   | 2 (10%)  | 4 (20%)         |         |
| Intestinal obstruction (n, %)   | 5 (25%)   | 4 (20%)  | 4 (20%)         |         |
| Mesenteric ischemia (n, %)      | 3 (15%)   | 2 (10%)  | 2 (10%)         |         |
| Subphrenic abscess (n, %)       | 0 (0%)    | 1 (5%)   | 1 (5%)          |         |
| Strangulated hæmia (n, %)       | 2 (10%)   | 2 (10%)  | 2 (10%)         |         |
| operative procedures            | 0.9       |          |                 |         |
| Simple repair (n, %)            | 3 (15%)   | 2 (10%)  | 2 (10%)         |         |
| Resection                       | 11 (55%)  | 10 (50%) | 9 (45%)         |         |
| Ileostomy (n, %)                | 3 (15%)   | 4 (20%)  | 3 (15%)         |         |
| Colostomy (n, %)                | 9 (45%)   | 8 (40%)  | 10 (50%)        |         |
| SOFA score (median, range)      | 10 (6–13) | 9 (6–13) | 9 (7–14)        | 0.5     |
| SAPS II score (median, range)   | 52.5 (32–64) | 54 (32–64) | 51 (41–64) | 0.8     |

Data are shown as mean ± SD, number (%), and median (range).

P < 0.05 was considered significant.

* = equal significant data.

Abbreviations: SD, Standard Deviation

BMI: Body Mass Index

SAPS: Sequential Organ Failure Assessment

SAPS: Simplified Acute Physiology Score

at 48 hours (Figure 2a), and similarly, dexmedetomidine reduced IL-1β level to a value lower than propofol and near equal to midazolam at 48 hours despite having significantly higher baseline value (Figure 2b).

8.3. Capillary leak index and lactate clearance

Dexmedetomidine caused a significant decline in capillary leak index through 48 hours compared to both midazolam and propofol (P < 0.05). Additionally, dexmedetomidine achieved significantly higher lactate clearance at 24 hours (P = 0.03) compared to both midazolam and propofol (Table 2).

8.4. Hemodynamic profile

Dexmedetomidine demonstrated significantly higher MAP readings (from 4 to 36 hours (Figure 3a), and significantly lower heart rate readings [from 2 to 24 hours (Figure 3b) compared to midazolam and propofol. CVP measurements and Norepinephrine equivalent dose were comparable between treatment groups through 48 hours.

Dexmedetomidine group had a significantly lower intake in the first 24 hours compared to propofol and midazolam, while in the next 24 hours and total 48 hours, intake was comparable between the three treatment groups (Figure 4). Dexmedetomidine group had significantly higher output and significantly lower positive fluid balance through 48 hours compared to midazolam and propofol (Figure 4).

8.5. ICU outcomes

Dexmedetomidine showed significant lower serum creatinine levels compared to both midazolam and propofol at 24 hours (Midazolam (median, range) 2.25 mg/dl (1.4–5.8), Propofol 1.95 mg/dl (1.3–3.5), Dexmedetomidine 1.6 mg/dl (1.3–3), P = 0.003) and 48 hours (Midazolam (median, range) 1.9 mg/dl (1.2–3.4), Propofol 1.65 mg/dl (1–3.4), Dexmedetomidine 1.6 mg/dl (1–1.3), P = 0.03). No significant differences had been detected between treatment groups as regards adverse events as hypotension (Midazolam (number, %) 13 (65%), Propofol 9 (45%), Dexmedetomidine 8 (40%), P > 0.05) and bradycardia (Midazolam (number, %) 0 (0%), Propofol 3 (15%), Dexmedetomidine 4 (20%), P > 0.05).

9. Discussion

The current study analysed IL-6 and IL-1β serum levels at different times in patients with abdominal sepsis, who underwent urgent abdominal surgery and were sedated and mechanically ventilated. Although dexmedetomidine showed numerically higher IL-6 and significantly higher IL-1β serum concentrations than
midazolam and propofol at baseline, it reduced their concentrations to near equal and lower levels at 48 hours than both midazolam and propofol. It is worthy saying that none of the studied patients was a chronic steroid user or had autoimmune diseases that require immune modulating therapies and that excludes the possibility of presence of confounders that may interfere with changes in serum cytokines levels of the studied patients. Additionally, dexmedetomidine showed a persistent reduction in CLI through 48 hours compared to both midazolam and propofol.

Ohta et al. [15] investigated the effects of dexmedetomidine versus non-dexmedetomidine sedation on sepsis-induced inflammation and vascular permeability in mechanically ventilated septic patients. Dexmedetomidine reduced CRP, procalcitonin, the incidence of hypoalbuminemia, and consequently capillary leak in the first 14 days in ICU. These findings were attributed to the ability of dexmedetomidine to inhibit inflammatory molecules expression upon binding to α2-adrenergic receptors on macrophages [16] as well as improved capillary permeability affected by inflammatory endothelial injury [17].

An earlier randomized prospective study by Tasdogan et al. [7] investigated the impact of intravenous infusion of dexmedetomidine and propofol on serum cytokine levels (TNF-α, IL-1, IL-6) in severely septic patients following abdominal surgery. They concluded that dexmedetomidine attenuated inflammatory response in contrast to propofol in septic patients during ICU sedation. Also,
Table 2. Capillary leak index (CLI) and Lactate clearance.

| Variable at admission | Midazolam | Propofol | Dexmedetomidine | P-value |
|-----------------------|-----------|----------|-----------------|---------|
| CLI at admission      | 8 (6–25)  | 7.5 (5–20) | 8 (5–21)       | 0.3     |
| CLI at 24 hours       | 7.5 (5–26) | 8 (5–24)  | 7.5 (5–18)     | 0.16    |
| Change of CLI at 24 hours | 7.5 (5–28) | 7 (4–23)  | 6.5 (4–19)     | 0.2     |
| Lactate at admission (mmol/L) | 5.6 (3–7)  | 5.7 (4–8)  | 5.4 (3–7)      | 0.7     |
| Lactate at 24 hours (mmol/L) | 4.9 (3–7)  | 5 (2–6)    | 4 (2–6)        | 0.1     |
| Lactate clearance at 24 hours (mmol/L) | 0.7 (1.6–1.9) | 1 (1.3–2.5) | 1.4 (1.3–2.2) | 0.03*   |
| Lactate clearance at 48 hours (mmol/L) | 0.8 (1.4–4.5) | 0.9 (2.6–3.7) | 0.8 (1.8–2.8) | 0.9     |

* denotes significance between groups (P < 0.05 was considered significant)

Data are shown as median (range).
P < 0.05 was considered significant.
* equal significant data

Figure 3. (a, b): Mean arterial blood pressure (MAP) and Heart rate over 48 hours.
Memiş et al. [8] showed that dexmedetomidine sedation alleviated the production of cytokines in sepsis compared to midazolam.

On the contrary to the current study, Venn et al. [18] and Elbaradie et al. [19] demonstrated comparable IL-6 serum levels when they compared dexmedetomidine versus propofol for short-term sedation in mechanically ventilated post-operative patients.

Significant changes in ILs activate MyD88 gene, which regulates endothelial permeability and thus contributes to vascular leak [20]. Zhang et al. [21] illustrated that dexmedetomidine inhibited the MyD88 gene in a rat sepsis model, leading to improvement of vascular stability and reduction in the capillary leak.

Also, She et al. [22] used an animal model of sepsis to find out whether dexmedetomidine is involved in protection of sepsis vascular leakage as well as the correlated underlying mechanism. The study demonstrated that dexmedetomidine efficiently alleviated sepsis vascular leakage and endothelial barrier dysfunction in septic rats via the protection of mitochondrial morphology and improving the mitochondrial function of vascular endothelial cells. Moreover, Lin et al. [23] showed negative effects of propofol on endothelial barrier in an animal model both in vivo and in vitro.

The current study showed that dexmedetomidine demonstrated higher MAP measurements with less intake and better lactate clearance during the first 24 hours compared to other groups. Additionally, comparable NEq dose was demonstrated among studied groups during study period.

In mechanically ventilated septic patients, Cioccarri et al. [24] compared the effect of dexmedetomidine sedation versus non-dexmedetomidine on hemodynamics and vasopressor requirements. The dexmedetomidine group showed numerically higher MAP readings, but not statistically significant. Nonetheless, the vasopressor requirements to achieve target MAP were significantly lower compared to the non-dexmedetomidine group. It was proposed that by lowering sympathetic outflow and reducing the release of endogenous catecholamines in sepsis, α₁-agonists were able to prevent down-regulation of α₁-adrenergic receptors and lead to their resensitization [25,26] and consequently improve the action of exogenous noradrenaline on vascular α₁ receptors [27]. However, Sigler et al. [28] observed higher use of vasopressors by dexmedetomidine sedated patients compared to propofol in mechanically ventilated septic patients.

Taman et al. [29] demonstrated lower intraoperative and postoperative total intake in the dexmedetomidine group versus placebo in patients undergoing partial hepatectomy. Moreover, Yu et al. [30] examined the impact of dexmedetomidine or propofol on preload dependency in patients with acute circulatory failure. Using fluid responsiveness indices, it was found that propofol infusion increased preload dependency by causing systemic arterial and venous vasodilation, and thus making relative central hypovolemia and preload reduction compared to dexmedetomidine. Also, in two animal models of sepsis in which...
10. Limitations

This study investigated serum IL-6 and IL-1β concentrations only as markers for inflammatory response. Evaluation of more sepsis biomarkers as TNF-α and procalcitonin as well as anti-inflammatory cytokines as IL-10 and IL-13 may be helpful in upcoming studies. Additionally, this study did not use the advanced dynamic modalities used in monitoring shocked patients and determining fluid responsiveness as trans-osophageal Doppler and arterial blood pressure waveform analysis due to unavailability. Finally, the wide variety of causes of abdominal sepsis with varying degrees of severity could attribute to the variability in serum baseline measurements of IL-6 and IL-1β among the studied patients.

11. Conclusion

Dexmedetomidine sedation in mechanically ventilated patients with abdominal sepsis reduced inflammatory response and capillary leak with better lactate clearance and less fluid intake. Additionally, the better hemodynamic profile with dexmedetomidine contributed to less positive fluid balance in this category of severely ill patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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