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Original Research Article

A clinical study on the effects of dexmedetomidine and propofol on erythrocyte deformability during anaesthesia

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Abstract

Purpose: *To investigate the clinical effects of dexmedetomidine and propofol on erythrocyte deformability (ED) in patients undergoing laparoscopic cholecystectomy.*
Methods: *A total of 522 patients undergoing gallbladder removal surgery were randomly divided into groups A (dexmedetomidine group), B (propofol group), and C (control). Erythrocyte suspensions were prepared from each group. Then, erythrocyte deformability index (EI) was measured in terms of RBC deformability. Moreover, endothelial nitric oxide synthase (eNOS) activity, and concentrations of nitric oxide (NO) were determined. Patients in the three groups received the same anaesthesia induction and maintenance, and their EI and Hct values were assayed before anaesthesia (T0) and post-surgery (T1). The activity of eNOS in each group was assayed using immunofluorescence microscopy and western blotting analysis.*
Results: *There were higher levels of EI and NO, and higher eNOS activity in erythrocytes in the dexmedetomidine group than in the propofol and ginsenoside groups ($p < 0.05$). Post-anaethesia EI (T0) values were higher in propofol and control groups than in dexmedetomidine group ($p < 0.05$). The protein expression of eNOS was higher in dexmedetomidine group, as was evident from immunofluorescence and western blotting analyses.*
Conclusion: *Perioperative use of dexmedetomidine during anaesthesia increases RBC deformability in vitro and directly upregulates eNOS activity in erythrocytes.*

Keywords: *Dexmedetomidine, Propofol, Erythrocyte deformability, Anesthesia*

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INTRODUCTION

General anaesthesia agents, stress, surgery, and other factors affect the cardiovascular system and microcirculation dynamics [1]. In fact, these agents change blood plasma rheology and impair tissue perfusion [2]. Alterations in perioperative hemorheology are also strongly associated with venous thromboembolism, microcirculatory damage, and other post-surgery complications [3, 4]. Changes in the viscosity of blood plasma are also linked to anaesthesia procedures responsible for deteriorations of tissue and organ perfusion [5]. In general, erythrocyte deformability and increased aggregation occur post-surgery under general anaesthesia [6,7].

Erythrocyte deformability (ED) is a condition in which the red blood cells change their morphological properties under the influence of external factors [8]. Its implications for successful microcirculation and normal body physiology depend on the deformability of healthy red blood cells. This is because, during carbon dioxide pneumatosis in laparoscopy operation, the pH of blood fluid generally decreases, and fluid effusion is reduced [9]. This leads to a decrease in oxygen transport capacity of the blood, reduction in microcirculation hypoperfusion, and impairment of red blood cell function. In fact, ED and plasma viscosity are two important factors that affect organ and tissue perfusion [10]. Deformability is defined as the capacity of erythrocytes to carry out oxygen transport, movement of vital molecules to their target organs and capillaries, and clearance of metabolic wastes.

Therefore, it is widely considered that drugs which enhance ED produce reduced complications among patients after surgery [11]. On the other hand, dexmedetomidine and propofol are widely used anaesthesia under monitored care, and their adverse effects require careful evaluation. Dexmedetomidine is an anxiolytic drug which acts as an agonist of α2-adrenergic receptors in the brain. It also produces sedation and pain relief [12]. Propofol is an anaesthetic agent frequently used for sedation and general anaesthesia.

Therefore, the present study was carried out to investigate the effectiveness of dexmedetomidine and propofol on ED, and to compare their protective outcomes in patients undergoing laparoscopic cholecystectomy in a stressed situation.

EXPERIMENTAL

Ethical approval and standards

All experiments were carried out in accordance with the Declaration of Helsinki 1964 and its later amendments. Consent in written form was given by all patients. Personal information, demographic factors and history of any medical episodes were recorded for each patient. The study was approved by the Research Review Ethics Board (RREB) of our Hospital. All protocols and procedures were approved by the RREB (approval reference: AKT/20170919 dated 19 June 2016), and also followed international guidelines for human studies.

Study population

A total of 522 patients scheduled for gallbladder excision surgery who opted for sedation were enrolled in this study. The patients were aged 21-55 years, with status 1 or 2 of the American Society of Anaesthesiologists (ASA). The patients had laparoscopic cholecystectomy between April 2018 to May 2021. Patients who had any episodes of neurological disorder, cardiovascular system, hypertensive and allergic to sedatives or analgesics, were not included in the study.

In vitro studies on erythrocytes

The eligible candidates were randomly assigned to ten different groups. Blood samples (5 mL each) taken from the patients were centrifuged at 1800 rpm in order to isolate the erythrocytes. The isolated erythrocytes were then washed with PBS solution and suspended in PBS at a volume ratio of 1: 49 (erythrocytes: PBS) to produce a 2 % suspension. For the analysis of erythrocytes, each of the 10 groups contained 2 mL of the erythrocyte suspension viz. low-concentration dexmedetomidine (DXL), low-concentration propofol (PPL), medium-concentration dexmedetomidine (DXM), medium-concentration propofol (PPM), high-concentration dexmedetomidine (DXH), high-concentration propofol (PPH), ginsenoside + dexmedetomidine (GID), ginsenoside + propofol (GIP), ginsenoside alone (GIN) and control.

Dexmedetomidine and propofol were added at levels of 0.6, 1.8 and 5.4 ng/mL corresponding to low, medium, and high concentration groups, respectively, while GID and GIP were used at concentrations of 0.2 *μ*mol/L and 1.7 ng/mL, separately or combined, depending on the group. Then, the drug-loaded erythrocyte suspensions were kept in a shaking incubator at 65 rpm and 36˚C for 90 min. Thereafter, RBC deformability was measured with a laser diffraction method using a Laser-assisted Optical Rotational Cell Analyser (LORCA, Mechatronics, Amsterdam, Netherlands). Then, the erythrocytes were treated with PVP solution and recorded when the “H” values were between 13 and 18 %. The ED was determined using erythrocyte deformation index (EI), whereas NO concentration in RBC was measured using nitrate reductase. The activity of eNOS was determined using Human eNOS/NOS3 ELISA Kit (Thermo Fisher Scientific, Pudong, Shanghai, China).

Clinical studies

The 522 patients who underwent gall bladder removal surgery were divided into 3 groups: A (n = 191), B (n = 173), and C (n = 158). Patients in groups A and B received dexmedetomidine and propofol, respectively, while those in group C served as control group. Prior to surgery, the baseline characteristics of the patients, such as pulse rate (PR), blood pressure (BP), electrocardiogram (ECG), pulse oximetry level (SpO2) and end-tidal carbon dioxide level ($PetCO_2$) were monitored and recorded till the completion of surgery. Patients in group A were administered intravenous infusion of 2 mL of dexmedetomidine diluted in 48 mL of physiological saline. The dose was controlled at 0.6 µg/kg for 12 min, using an infusion pump. Group B patients were administered an intravenous infusion of 3 mL of propofol diluted in 47 mL physiological saline. In this case, the dose was maintained at 0.4 µg/kg for 12 min with the help of an infuser. Then anaesthesia was induced with midazolam at a dose of 0.04-0.06 µg/kg and sufenanil at a dose of 0.3-0.6 µg/kg, *via* slow IV injection after oxygenation.

Tracheal intubation was facilitated with *i.v*. administration of cisatracurin (0.14 mg/kg). In groups A and B, anaesthesia was given till the end of ketamine and remifentanil administrations at doses of 2-6 mg/kg/h and 0.2-0.8 µg/kg/h, respectively. Group C (control) was given saline in place of dexmedetomidine anaesthesia. Hemodynamic events and blood flow were recorded by an anaesthesiologist. The reversal of neuromuscular blockage was attained *via* administrations of neostigmine and glycopyrrolate at doses of 0.06 and 0 µg/kg, respectively. In addition, EI and hematocrit (Hct) were recorded before anaesthesia (T0) and evaluated just after the surgery (T1). The measurement of Hct i.e., volume percentage (vol %) of red blood cells (RBC) was carried out using a Hematocrit BioBase Blood Biochemistry Analyzer (Biobase Biozone Co. Ltd, Quingdao, China), while EI was evaluated by measuring changes in blood flow from the opposite extremity position of *i.v.* administration at T0 and T1 using a Full-automated self-cleaning Haemorheology Analyzer (LBYN6B, Beijing Precil, China).

eNOS estimation

The RBCs from the patients in groups A, B and C were obtained using differential centrifugation. Then, eNOS was immuno-labeled using a rabbit polyclonal antibody obtained from Shanghai Life Science, China. immunofluorescence staining was carried out by fixing the RBC samples from the three groups in 3 % PFA solution and 0.2 M PBS solution containing 2 % BSA. The samples were further permeabilized with Tween 20 and immuno-labeled with the eNOS antibodies. The preparations were further washed with de-ionized water and incubated with anti-rabbit antibodies for 45 min, after which they were mounted on a fluorescence microscope (Leica, Wetzlar, Germany) and examined.

Western blotting

Total proteins were extracted from the RBC samples obtained from the three groups of patients. The protein expression levels of eNOS were determined using western blotting technique. Equal amounts of protein (approximately 70-µg samples) were resolved using 1 % SDS-PAGE at 140 V for 70 min in 20 mM Tris-glycine buffer. The proteins were then transferred to nitrocellulose membranes using a Trans-Blot Turbo Transfer System (BioRad) for 10 min, followed by incubation with eNOS antibody. The immunoreactive bands were detected and quantified using SuperSignal West Atto (ThermoFisher Scientific, Pudong New Area, Shanghai, China). The bands were visualized using iBright FL1500 Imaging System (ThermoFisher Scientific, Pudong New Area, Shanghai, China).

Statistical analysis

Statistical analysis was carried out using SPSS 18.0 (SPSS Inc, USA). All results are expressed as mean ± standard error of the mean (SEM). Data were compared between groups using *t*-test, while multiple group comparisons were done using two-way ANOVA. Values of $p < 0.05$ were indicative of statistically significant differences.

RESULTS

RBC deformability

Table 1 shows RBC deformability based on EI values. There were higher EI value, higher NO levels and higher eNOS activity in erythrocytes in DXL, DXM and DXH (dexmedetomidine groups) than PPL, PPM and PPH (propofol groups) and the control group. A higher EI value is a sign of better ED. All the concentrations of dexmedetomidine used *viz* DXL, DXM and DXH, produced significantly higher EI values, NO concentrations and eNOS activity than the other groups ($p < 0.05$). In contrast, ginsenoside did not affect the level of EI, NO concentration and eNOS activity ($p > 0.05$). However, it resulted in

higher values of EI, NO, and eNOS activity when mixed with dexmedetomidine ($p < 0.05$).

On the other hand, clinical investigation of the three groups of patients revealed that post-anaesthesia values of EI (T1 values) were higher in group B (propofol) and group C (control) than in group A (dexmedetomidine), as shown in Table 2. The larger the EI value, the poorer the ED which was evaluated by viscosity measurement. However, no statistical significances were observed in HCT and EI values amongst the three groups at T1 and T0 ($p > 0.05$). Moreover, EI at T1 (0.93±0.12) was higher than EI at T0 (0.81±0.21) in group B, when compared to the corresponding values in the other two groups. However, there were no statistically significant differences in Hct and EI values between T0 and T1 in group A ($p > 0.05$). These data are shown in Table 2.

From Figure 1, it is also evident that the expression level of eNOS protein was up-regulated in group A (dexmedetomidine group), when compared to group B (propofol group) and the control group. In fact, the eNOS protein was highly expressed in the RBCs of group A (dexmedetomidine group) patients, with a distinct ring of eNOS immunofluorescence surrounding the cytoplasm (Figure 1A). In contrast, there was little or no eNOS protein expression in the control and group B (propofol) patients (Figures 1B and 1C, respectively). In addition, western blot assay revealed eNOS-specific protein expression in the RBCs of group A (dexmedetomidine group) which was evident from the distinct band at 140 kDa (Figure 2A, lane-1). This band was absent in group B and control group (Figure 2, lane 2 and lane 3).

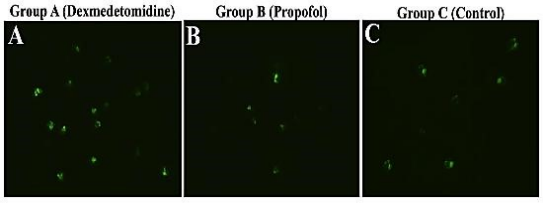

Figure 1: Detection of eNOS protein among patients of groups A, B and C using immunofluorescence microscopy. There was abundance of eNOS in group A, whereas there was little or no eNOS in groups B and C

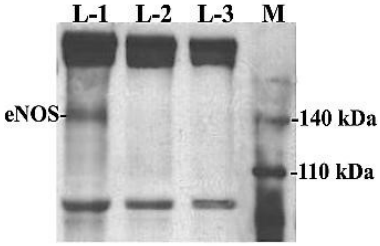

Figure 2: The eNOS-specific protein band was seen in group A (L-1) at 140 Kda, whereas no band was observed in group B (L-2) and group C (L-3)

DISCUSSION

Results from *in vitro* analysis revealed that dexmedetomidine at high, medium, and low doses increased NO level and eNOS activity, when compared with high, medium, and low doses of propofol.

Table 1: EI values, NO levels and eNOS activity in erythrocytes in the three groups of patients

Group	Erythrocyte Indices (%)	NO (μmol/g HB)	eNOS (U/mg HB)
CON	20.67±1.23	5.78±0.42	20.68±1.76
DXL	24.76±2.05[a]	5.89±0.76[a]	26.04±2.12[a]
PPL	20.45±1.45	3.89±0.54	18.75±1.98
DXM	26.12±1.83[a,b]	6.12±0.94[a,b]	26.81±2.65[a,b]
PPM	21.87±1.45	4.16±0.31	20.691.67
DXH	26.45±1.43[a]	6.34±0.45[a]	27.85±3.23[a]
PPH	22.05±1.97	4.84±0.86	22.34±1.76
GIN	19.84±1.34	4.67±0.66	21.74±1.23
GID	23.34 ±1.43[a]	5.45±0.54[a]	22.62±1.87[a]
GIP	20.41±1.13	4.81±0.32	21.84±2.54

[a]$P < 0.05$, compared with groups B and C; [b]$p<0.05$, compared with groups A and C

Table 2: Values of EI and Hct in the three different groups of patients

Groups	Erythrocyte Indices (%)		Hematocrit & Hct value (l/l)	
	T0	T1	T0	T1
A (Dexmedetomidine)	0.83±0.12	0.86±0.14	0.39±0.24	0.38±0.11
B (Propofol)	0.81±0.21	0.93±0.12[a]	0.36±0.22 [a]	0.35±0.18 [a]
C (Control)	0.82±0.17	0.90±0.22[b]	0.38±0.16	0.37±0.23 [b]

[a]$P < 0.05$, compared with groups B and C; [b]$p < 0.05$, compared with groups A and C

Thus, dexmedetomidine directly improved the deformability of RBCs. Ginsenoside which is present in ginseng, did not produce any beneficial effect on erythrocyte deformability when it was given alone. However, it showed some beneficial effects when mixed with dexmedetomidine, as was evident in slight increases in ED. Ginsenoside did not produce any beneficial effect on the deformability of red blood cells when mixed with propofol, indicating that dexmedetomidine was better than propofol in the enhancement of red blood cell deformability. In the present study, special attention was given to laparoscopic cholecystectomy patients based on the observation that the hemorheology of these patients was drastically altered after pneumoperitoneum, relative to preoperative hemorheology [13].

It has been reported that EI which is based on the viscosity method, is generally affected by Hct [14]. However, in the present study, there were no significant changes in Hct of the dexmedetomidine group before and post-surgery, when compared to group B (propofol) and control group. Thus, Hct had no effect on EI. However, E1 values in group B (propofol) and group C (control) were markedly higher at T1 than at T0, which indicates that ED values of patients in these two groups were gradually and significantly decreased post-surgery. In contrast, there was no marked difference between E1 value at T0 and E1 value at T1 in group A, due to the perioperative use of dexmedetomidine which mitigated ED that was damaged during surgery and anaesthesia. The perioperative use of dexmedetomidine maintains stability in perioperative blood rheology of the patients [15,16].

The findings in the present investigation are in agreement with the results obtained in an animal study in which it was observed that dexmedetomidine improved ED in a Wistar albino rat model [17]. It was also reported that dexmedetomidine exerted protective effect against hepatic I/R injury-induced lipid peroxidation, thereby revealing the potential role of dexmedetomidine in ED [17].

Nitric oxide (NO) molecules are also crucial in ED as free radicals which are involved in cell signaling and other physiological effects [18]. They usually regulate and maintain RBC deformability. It has been reported that NO interacts with β93Cys residues of haemoglobin to produce S-nitrosohemoglobin, thereby increasing ED [19]. Therefore, there is a requirement for optimum concentration of NO in erythrocytes for maximum deformability [20]. In the present study, the NO levels in the low, medium, and high dexmedetomidine groups, and eNOS activities were elevated, resulting in improved ED values. Dexmedetomidine acts on α2 adrenergic receptors of the endothelial cells which activate eNOS, thereby increasing NO levels in the body [21]. Endothelial nitric oxide synthesis contributes significantly to the net responses of human peripheral blood vessels when infused with dexmedetomidine in appropriate clinical doses [22]. In China, ginsenoside has been used as a traditional herbal medicine. However, studies have shown that it attenuated α2 adrenergic receptors in animal models [23].

In the present study, there were no improvements in ED when ginsenoside was used, either alone, or mixed with propofol. Moreover, propofol which is frequently used for sedation and general anaesthesia, has been reported to increase the relative resistance to ED in a rat model study, thereby causing functional deteriorations in blood flow and tissue perfusion [24]. In general anaesthesia during surgery, alterations in blood rheology are generally observed, and these changes are among the factors responsible for impairment of tissue and organ perfusion related to anaesthetic procedures. This may be due to preoperative factors, use of narcotics, and transfusion. Therefore, drugs like dexmedetomidine which increase ED are vital in clinical practice. This study also found that eNOS protein is important in ED and aggregation of platelets. There was high level of eNOS in patients treated with dexmedetomidine, when compared to those treated with propofol, as was evident from immunofluorescence microscopy and western blotting analysis. Thus, dexmedetomidine produced a better RBC deformability than propofol.

CONCLUSION

This study has shown that the use of dexmedetomidine during anaesthesia increases RBC deformability *in vitro*. Moreover, perioperative use of dexmedetomidine radically enhances ED of patients following gallbladder removal surgery. In contrast, propofol impairs ED, and this may lead to negative alterations, result probably in functional disorders in blood flow and tissue perfusion. Thus, dexmedetomidine may potentially improve EI, when compared to propofol. In fact, dexmedetomidine has a direct up-regulatory effect on eNOS, thereby enhancing the concentration of NO in RBCs.

DECLARATIONS

Acknowledgement

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Xiang Cui, Ling Ma, conceived and designed the study, Xiang Cui, Ling Ma, Jingfang Wei collected and analysed the data. Xiang Cui, Ling Ma and Jingfang Wei, a draft and wrote the manuscript. Xiang Cui, Ling Ma contributed to this work equally.

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