

CARDIOVASCULAR CHANGES ASSOCIATED WITH INFUSION OF HEMATOPOIETIC CELL GRAFTS IN ONCOHEMATOLOGICAL PATIENTS — IMPACT OF CRYOPRESERVATION WITH DIMETHYLSULFOXIDE

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Aim: Dimethylsulfoxide (DMSO) is the most frequently used agent for hematopoietic cell (HC) graft cryopreservation. This study aimed to monitor blood pressure and heart rate (HR) during HC graft infusion and assess the impact of cryopreservation with DMSO. **Methods:** 153 HC graft infusions in 153 consecutive hematological patients (mean age 49.1 ± 12.6 years; 80 males) were evaluated. Cryopreservation with DMSO was used in 133 grafts (DMSO group). Twenty grafts were infused directly without cryopreservation (control group). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were measured immediately before and after HC graft infusion. **Results:** SBP and DBP increased significantly after graft infusions cryopreserved with DMSO ($p < 0.0001$ for SBP; $p < 0.01$ for DBP). Increases (> 10 mmHg) in SBP were seen in 42 (31.6%) patients; in DBP in 31 (23.3%) patients. Changes in HR were non-significant in DMSO group. Increases in BP and HR correlated with increasing DMSO dose ($p < 0.01$; $p < 0.05$, respectively). Changes in SBP, DBP and HR were non-significant in control group. **Conclusion:** HC graft infusions cryopreserved with DMSO could cause statistically significant increases in SBP and DBP, without changes in HR. These changes were mostly transient and asymptomatic, not requiring therapeutic intervention. However, they might cause complications, especially in patients with preexisting cardiovascular disease, who should be monitored closely during HC transplantation. **Key Words:** dimethylsulfoxide, cryopreservation, transplantation, blood pressure, heart rate.

Dimethylsulfoxide (DMSO) is a chemical compound with a formula $(\text{CH}_3)_2\text{SO}$. DMSO has been used as a solvent in biological studies and as a vehicle for drug therapy for a long time [1, 2]. Since 1990, DMSO has been the most frequently used substance for cryopreservation of hematopoietic cell (HC) grafts [3–5]. The cryopreservation solution usually contains 10% DMSO and 2–4% albumin or autologous plasma. The grade of toxicity experienced by patients when cryopreserved HC grafts are infused is related to the amount of DMSO present in the HC concentrates. Recently, some institutions have started using 5% DMSO as cryoprotectant for the autologous HC grafts [6, 7]. The maximum recommended daily dose of DMSO is 1 g/kg of the recipient body weight due to dose-dependent side effects. The most common side effects of DMSO include nausea, vomiting, diarrhea, rashes, bronchospasm, headache and cardiovascular changes [8–10]. DMSO may lead to changes in blood pressure (BP) and heart rate (HR). In most studies, increase in BP and decrease in HR were found [2, 11, 12]. However, decrease in BP or increase in HR or no changes in BP and HR were reported in several studies and the results are inconsistent [9, 13]. Thus, the

European Group for Blood and Marrow Transplantation (EBMT) has recently launched a multicenter study on monitoring of side effect of DMSO including cardiovascular changes (so called “DMSO Toxicity Study”). The results of the study have not been published yet.

The aim of our study was to monitor BP and HR during HC graft infusions and to assess the effect of DMSO cryopreservation on these parameters in patients transplanted for a hematological disease in our transplant center (Department of Medicine II, Clinical Hematology, University Hospital Hradec Kralove, Czech Republic).

We evaluated 153 HC graft infusions in 153 consecutive hematological patients. The patients consisted of 80 males and 73 females with the mean age of 49.1 ± 12.6 years. Forty-two patients were treated for arterial hypertension and were well compensated before HC transplantation. Cryopreservation with DMSO was used in 133 (86.9%) grafts, 20 (13.1%) grafts were infused directly without cryopreservation (control group). One hundred and fifteen (75.2%) grafts were autologous and 38 (24.8%) allogeneic (from that 18 matched unrelated donor transplants). The most frequent diagnoses were multiple myeloma (55 patients), non-Hodgkin's lymphoma (35 patients) and acute myeloid leukemia (29 patients).

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured immediately before and after HC graft infusion. Changes (either increase or decrease) in SBP or DBP by more than

Received: May 5, 2009.

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Abbreviations used: BP – blood pressure, DBP – diastolic blood pressure, DMSO – dimethylsulfoxide, HC – hematopoietic cell(s), SBP – systolic blood pressure, HR – heart rate.

10 mmHg or changes in HR by more than 10 beats/min were considered significant in our study.

Statistical analysis was performed with the “Statistica for Windows, Version 5.0” program. Paired two tailed *t*-tests and McNemar tests were used. The values are expressed as mean \pm standard deviation (SD). Probability values $p < 0.05$ and lower were considered statistically significant.

The results are shown in Table 1 and Table 2. SBP and DBP increased significantly just after graft infusions cryopreserved with DMSO. Increase in SBP by more than 10 mmHg was seen in 42 (31.6%) patients, in DBP in 31 (23.3%) patients. Moreover, the increase in BP and HR correlated with the increasing DMSO dose — changes were more pronounced in patients with the total DMSO dose above 0.8 g/kg of recipient body weight ($p < 0.01$, $p < 0.05$ respectively). In the control group without DMSO cryopreservation, the changes in SBP, DBP and HR were not significant. Changes in SBP, DBP and HR were not significantly different in patients treated for arterial hypertension in comparison with the other patients.

Table 1. Changes in blood pressure and heart rate during hematopoietic cell graft infusion with dimethylsulfoxide ($n = 133$)

Parameters	Before HCT	After HCT	<i>p</i>
SBP (mmHg)	122.3 \pm 17.9	127.7 \pm 18.1	< 0.0001
DBP (mmHg)	70.9 \pm 12.3	74.1 \pm 12.6	< 0.01
HR (/min)	81.5 \pm 13.6	81.8 \pm 14.2	NS

In Table 1 and Table 2: HCT – hematopoietic cell transplantation.

Table 2. Changes in blood pressure and heart rate during hematopoietic cell graft infusion without dimethylsulfoxide ($n = 20$)

Parameters	Before HCT	After HCT	<i>p</i>
SBP (mmHg)	136.3 \pm 17.6	138.4 \pm 15.6	NS
DBP (mmHg)	78.1 \pm 9.5	76.9 \pm 11.3	NS
HR (/min)	81.6 \pm 23.0	81.1 \pm 21.8	NS

Our results on 153 consecutive hematological patients show that only HC graft infusions cryopreserved with DMSO caused statistically significant increases in SBP and DBP. In our study, significant increases (by more than 10 mmHg) in SBP were found in 31.6% patients, in DBP in 23.3% patients. Changes in HR were not statistically significant. These changes were mostly transient and asymptomatic and did not require therapeutic intervention. However, they might cause complications, especially in patients with preexisting cardiovascular disease (amyloidosis with cardiac involvement, chemotherapy-induced cardiomyopathy, coronary artery disease, cardiac arrhythmia, not adequately compensated arterial hypertension prior to HC transplantation, etc.). The patients at risk for cardiovascular complications should be monitored closely during cryopreserved HC graft infusion, e.g. continuous monitoring of ECG and BP.

To reduce the side effects of cryopreservation agent DMSO, the amount of infused DMSO could be decreased by centrifugation right before the HC graft infusion [14]. The drawback of this procedure is a significant loss of HC (according to our experience up to 30%) which may result in delayed engraftment. Another possibility is to fractionate the application of HC

graft in more consecutive days and thereby reduce the total daily DMSO dose and toxicity [15].

To conclude, HC graft infusions cryopreserved with DMSO could cause statistically significant increases in SBP and DBP, without changes in HR. Patients with preexisting cardiovascular disease should be monitored closely during HC transplantation. Alternatively, the amount of DMSO could be depleted before HC graft infusions.

ACKNOWLEDGMENTS

The work was supported by research projects MO 0FVZ 0000503 (Czech Ministry of Defence) and MZO 00179906 (Czech Ministry of Health).

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