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Risk of Reperfusion Injury in Isolated Hyperthermic Limb Perfusion

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Abstract

Aim: Isolated hyperthermic limb perfusion (IHLP) is a standard treatment method for selected patients with local recurrence of melanoma with frequent in-transient metastases in the lower or upper limb, and for selected patients with advanced soft tissue sarcomas of the extremity. Extremely high concentrations of cytotoxic drugs administered during perfusion, hyperthermia and hypoxia followed by reoxygenation during the procedure are potential risk factors for development of compartment syndrome. The presented study addresses safety of the procedure with respect to compartment syndrome, assessing several biochemical parameters in blood sampled from the perfused limb.

Methods: In the time period from September 2009 till December 2010 we performed a total of 20 cytostatic IHLP in 17 patients. Metabolic (lactate, base excess, pH) and haematological parameters (haemoglobin, hematocrit) were measured in the blood of perfused extremity. Risk of compartment syndrome was estimated according to our previous study on acute limb ischemia.

Results: In the short term, no serious complications were associated with the procedure. Postoperative swelling and erythema of grade 2 to 3 according to Wieberdin's classification were present in most of the patients. However, markers of tissue damage and reperfusion injury did not exceed limits indicating risk of compartment syndrome or severe systemic complications.

Conclusion: The affected limb is exposed to extreme conditions that lead to significant changes of local metabolism. However, despite the hypoxia during the procedure, these transient alterations do not lead to a clinically significant compartment syndrome or to severe systemic complications. Thus, IHLP can be considered a safe treatment modality in selected patients.

Keywords: Isolated hyperthermic perfusion; Melanoma; Compartment syndrome; Melphalan; Reperfusion injury

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Introduction

Isolated hyperthermic limb perfusion (IHLP) is a treatment method for selected patients with local recurrence of melanoma with frequent in-transient metastases in the lower or upper limb, and for selected patients with locally advanced extremity soft tissue sarcomas, without evidence of distant metastases [1]. The procedure consists of isolation of the affected extremity from the systemic blood circulation and its connection to an extracorporeal blood circuit. The limb is then perfused with a hyperthermic solution containing the blood from the extremity vessels, priming solution used to fill up the extracorporeal circuit and medication (cytostatic drugs). The extracorporeal circuit contains an oxygenator in order to ensure gas exchange in the perfused tissues. This procedure can achieve extreme tissue concentration of the cytostatic compared to the maximum achievable concentration in systemic administration [2]. The use of particular types of cytostatic and their combination brings further improvements in therapeutic results [3]. The aim of our study was to evaluate the metabolic effects of isolation of the limb from the systemic circulation and its perfusion with heated cytostatic. During the procedure, tissues of the isolated extremity are exposed to extreme conditions. These involve hypoxia due to decreased haemoglobin concentration (dilution of blood with the priming solution), hyperthermia, high concentration of cytotoxic drugs and different concentration of ions

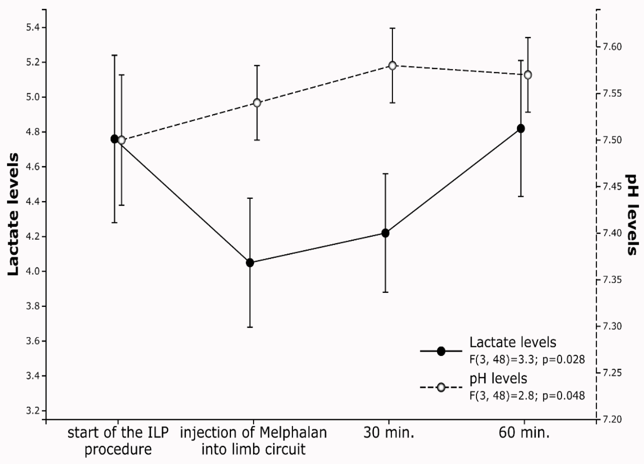

Figure 1: Arterial blood lactate and pH in isolated limb during ILP.

in the perfusate. Along with subsequent re-connection of the limb to the systemic circulation, metabolic changes resembling the ischemia-reperfusion injury, e.g. increase in lactate concentration and acidosis, ensue. Other cases of ischemia-reperfusion injury to a limb, e.g. caused by embolism followed by embolectomy, can result in threatening complications like a severe compartment syndrome of the limb and systemic inflammatory response with multi-organ failure. In this pilot study, we analyzed the use of IHLP in patients with malignant melanoma (MM). All patients underwent IHLP without the use of TNF alpha. Metabolic parameters were compared and contrasted to a dynamics in ischemic-reperfusion injury after embolectomy [4-7]. Based on this analysis the risk of severe compartment syndrome development was assessed.

Materials and Methods

Between September 2009 and December 2010 17 patients were treated by IHLP at the 2nd Surgical Department of Cardiovascular Surgery, Prague, Czech Republic. Preoperative, perioperative and postoperative samples of selected parameters of internal environment including blood gases were collected.

Out of 17 patients, 3 patients underwent repeated procedure in order to extend the indication for the continuation of the treatment due to the favorable effect of the therapy (N=17, M=3, 1 × repeated, F=14, 2 × repeated). Metabolic parameters (lactate, base excess, pH) and haematological parameters (haemoglobin, hematocrit) were measured in blood samples from both the limb and the systemic circulation before isolating the limb, during its isolation, after reconnecting the limb to the systemic circulation and subsequently 2, 6, 12 and 24 hrs after the surgery. The systemic blood was drawn from the radial artery. The blood from the limb was sampled from the arterial part of the extracorporeal circuit during isolation of the limb.

Stöckert S3 (S5) - heart-lung machine, the Medos Hilite® 2800-Series Oxygenator, the Sechrist gas mixer, the Stöckert cooling and heating unit, and Polystan's arterial and venous cannula were used for the perfusion.

ILP cannulation technique and ILP parameters

The technical execution of the operation consists of dissecting the blood vessels of the affected limb and their subsequent cannulation in order to institute extracorporeal circulation. The site of the cannulation depends on the tumor location, metastasis, and targeted area for perfusion. For tumors located in the middle of the thigh we had utilized femoral vessels for cannulation. For tumors approaching the upper thigh area up to the area of the inguinal junction, iliac vessels were selected for cannulation. In a case of iliac vessels cannulation, we have consistently chosen an extra-peritoneal approach. Isolation of the collateral circulation should be done in this case using temporary external fixation. Similarly, the cannulation sites of the upper limb depend on the tumor localization. The cannulation of the respective vessels is performed through diagonal incision; the diameter of the cannula is selected according to the diameter of the vessels in order to ensure sufficient flow in the extracorporeal circulation.

The OTC (Over-the-Counter) device is an oxygenator mounted circuit providing gas exchange in the bloodstream to limit the risk limb ischaemia as low as possible during perfusion. The heat exchanger ensures the necessary heating of the solution so that the target tissue temperature reaches 39°C to 40°C. The target temperature monitoring is continuously monitored by the muscular and subcutaneous thermo sensors. The limb was rinsed in a sterile water-plate to facilitate local hyperthermia. The standard heating time attained approximately 30 mins. Once reaching the target temperature, on site prepared cytostatic solution (Melphalan/ Alkeran) was added to the perfusate in a dosage corresponding with the calculated limb volume. Prespecified cytostatic perfusion time was 90 mins. Then, the limb was perfused with 2 liters of isotonic solution in order to eliminate the perfusate from the limb. The perfusate was disposed off according to the guideline manipulation with biological material and cytostatics. Potential leakage of perfusate with cytostatic was monitored by nuclear medicine detection.

Statistical analysis

Parameters obtained during the measurement of selected metabolic and haematological parameters were subject to a statistical analysis. Data were first tested for normality using the Kolmogorov-Smirnov test. Normal distribution of the vast majority of the variables allowed for a use of parametric tests to analyze repeated measurements. Analysis of variance (ANOVA) with repeated measurements was used to test the equality of means over time. In order to compare all pairs of means, Fisher's post-hoc test was used. The statistical significance of means was tested at three levels ($p<0.05$, $p<0.01$ and $p<0.001$). All calculations were performed in SPSS (version 17.0). The charts were made in Statistica (version 9.0).

Results

Lactate concentration, pH, base excess (BE), haemoglobin concentration (Hb) and haematocrit (Hct) were monitored in full arterial blood drawn from both systemic circulation (values marked "Syst.", from radial artery) and the limb perfused by extracorporeal circulation ("Limb", from the output of the oxygenator). In the isolated limb perfused with extracorporeal circulation with an oxygenator, significant changes in all monitored parameters were observed during the procedure. The lactate concentration in the limb decreased after commencing of the extracorporeal circulation due to dilution of the circulating blood with the priming solution (Figure 1). Decrease of Limb-lactate corresponds to the decrease of Limb-Hb and Limb-Hct. At the time of cytostatic administration (time 0 minutes in Figure 1), Limb-Hb and Limb-Hct dropped down to 54% and 55% of original values (i.e. values before limb isolation).

During the procedure of IHLP, limb-lactate was continuously growing.

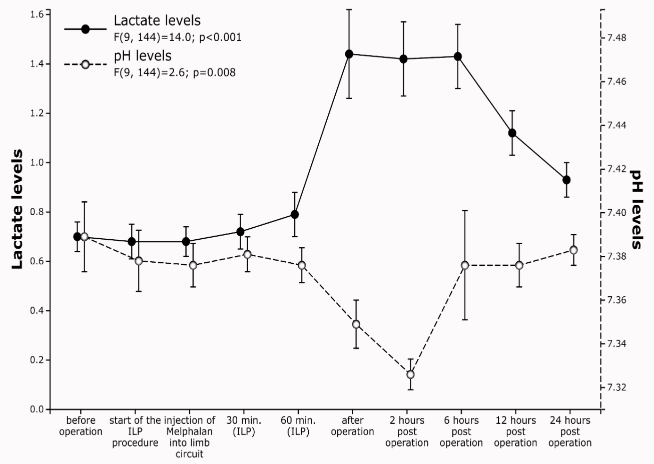

Figure 2: Lactate and pH levels in systemic circulation of patient during ILP procedure.

The lactate concentration in the systemic circulation changed significantly, too. However in a different pattern: It remained unchanged during the whole period of the limb perfusion on the extracorporeal circuit. Notably, Syst-lactate increased significantly after reconnection of the limb to the systemic circulation (Figure 2). Accordingly, Syst-pH rapidly decreases when the limb perfusion with systemic blood was restored. These data show that in the time of IHLP the tissues of the limb suffer from hypoxia as reflected by lactate acidosis. A substantial amount of lactate is consequently washed out from the limb to the systemic circulation.

In the analysis of the ten repeated measurements in the systemic circulation, the mean variations in the Lactate-C variables ($p<0.001$), pH-C ($p=0.008$), BE-C ($p<0.001$) haemoglobin-C ($p<0.001$), and haematocrit-C ($p<0.001$) were different and statistically significant. In the case of extracorporeal circulation, the mean of four repetitive measurements for the variables Lactate-OX ($p=0.028$), pH-OX ($p=0.048$), haemoglobin-OX ($p=0.007$) and haematocrit were significantly different as well. Differences in the BE-OX variables were not statistically significant ($p=0.883$) (Figure 2). Post-hoc tests has shown that the mean values of the lactate-C variable are statistically significantly different from those measured before the extracorporeal circulation (EC) and the following three measurements after procedure ($p<0.001$), 12 hrs after the operation, the return to the EC ($p<0.05$) and 24 hrs after the operation. Some differences are not statistically significant. In the case of the lactate-OX variable, the mean infusion rates differ from baseline EC ($p=0.022$) and from 60 min from infusion ($p=0.014$).

A similar pattern as pH-C has been shown BE-C variable. Average values decrease over time and the minimum occurs after EC, averages being statistically significantly different from all other values at this minimum ($p<0.01$). From this point on, the baseline returns as evidenced by the fact that differences in the averages before EC and 24 hrs after surgery are not significant ($p=0.752$) (Figure 1).

The results had also shown that an overlapping time course of the mean values of the haemoglobin-C and haematocrit-C variables. Parameters before EC are statistically significantly higher than the remaining 9 measurements for both haemoglobin-C ($p<0.001$) and haematocrit-C variables ($p<0.01$). For both variables, the lowest mean values are observed 2 hrs after the surgery, followed by an increase. In the case of the haemoglobin-C measures, the mean value returns to the second measurement level (when EC is started) ($p=0.438$). The haematocrit-C variable returns only to the third measurement level ($p=0.183$). Similarly, with the haemoglobin-OX and haematocrit-OX variables, there is a similar, growing trend. Mean haemoglobin-OX values 60 min from infusion significantly differ from the 30-minute infusion ($p=0.037$), infusion ($p=0.009$) at MO ($p<0.001$). The mean haematocrit-OX values taken 60 mins after the infusion are then different from the infusion ($p=0.012$) and EC start ($p=0.004$).

Discussion

During IHLP, the perfused limb is subjected to extreme conditions in terms of local metabolism [1,6]. Due to the isolation of the limb there is a temporary absence of autoregulatory metabolic mechanisms [8]. Hyperthermia has an unambiguous burden on limb muscles [1,3,8] and together with substantial dilution of blood in the limb with the priming solution in extracorporeal circulation, it inflicts hypoxia of the limb. In our study, hypoxia was demonstrated especially by rapid increase in lactate concentration. At the end of IHLP, the extremity is reconnected to the systemic circulation again. Reperfusion with blood well saturated with oxygen causes reperfusion injury.

Reperfusion of the limb of a particular concern. The major risk is that reperfusion injury can lead to severe compartment syndrome [9]. This occurs e.g. in some patients with acute limb ischemia due to embolism after embolectomy. That is why Schmidt et al. suggest specific regimens of reperfusion with the use of hypothermic, initially low-oxygen blood perfusion [10]. In previous study we have shown that severe compartment syndrome in acute limb ischemia can be predicted by difference in lactate concentration before and after embolectomy [11]. Difference greater than 3 mmol/L indicates high risk of severe complications.

In the present study, differences in lactate concentrations during ILP were in all events substantially smaller. Our observations suggest that despite considerable and well demonstrated metabolic changes during procedure, IHLP seems to be safe in a perspective of the compartment syndrome induction as also corroborated by its complete clinical absence in the study cohort.

Conclusion

Despite evident ischemic changes during IHLP, this method can be considered safe with respect to severe ischemia-reperfusion injury. The risk of compartment syndrome, a major complication of limb reperfusion remains very low.

The observations expand the knowledge on metabolic changes in the limb ischemia-reperfusion injury and underlying pathophysiological background.

Author Contributions

All of the authors of this manuscript are responsible for the reported findings. MP, HG, SR, ŠM collected all clinical data of practical approach and was responsible for the therapeutic process. MP and NR were responsible for writing draft of the manuscript, VM was responsible for interpretation of biochemical results, All authors participated in the searching of the published literature for this review; analysis and interpretation of the data; drafting and/or revising and/or making intellectual contributions to the content of the manuscript; PO was responsible for statistical analysis of collected data, HJ, MŠ and LJ approved the final version of the manuscript submitted for publication.

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