

INTRODUCTION

High-dose methotrexate (HD-MTX) is used in cancer treatment, with serum MTX concentration monitoring to minimize toxicities including oral mucositis (OM). This study aimed to evaluate the correlation between serum and salivary MTX concentrations, the relationship between salivary MTX and OM, and photobiomodulation therapy (PBMT) effectiveness in preventing OM.

METHODS

A randomized, double-blind, prospective study was conducted on onco-hematological adult patients receiving their first HD-MTX cycle. Patients were assigned to Group A (prophylactic PBMT 660nm, 100mW, spot size 0.028cm², 1J per point/10s) or Group B (sham laser). PBMT was applied to the oral mucosa for 5 days after infusion, or until MTX serum concentrations were <5 µmol/L (24h), <1 µmol/L (48h), and <0.1 µmol/L (72h). Serum and salivary MTX concentrations were measured at 24, 48, and 72 hours after infusion. OM severity was classified using WHO criteria. Logistic, multinomial, and robust-error-variance Poisson regression analysis were used.

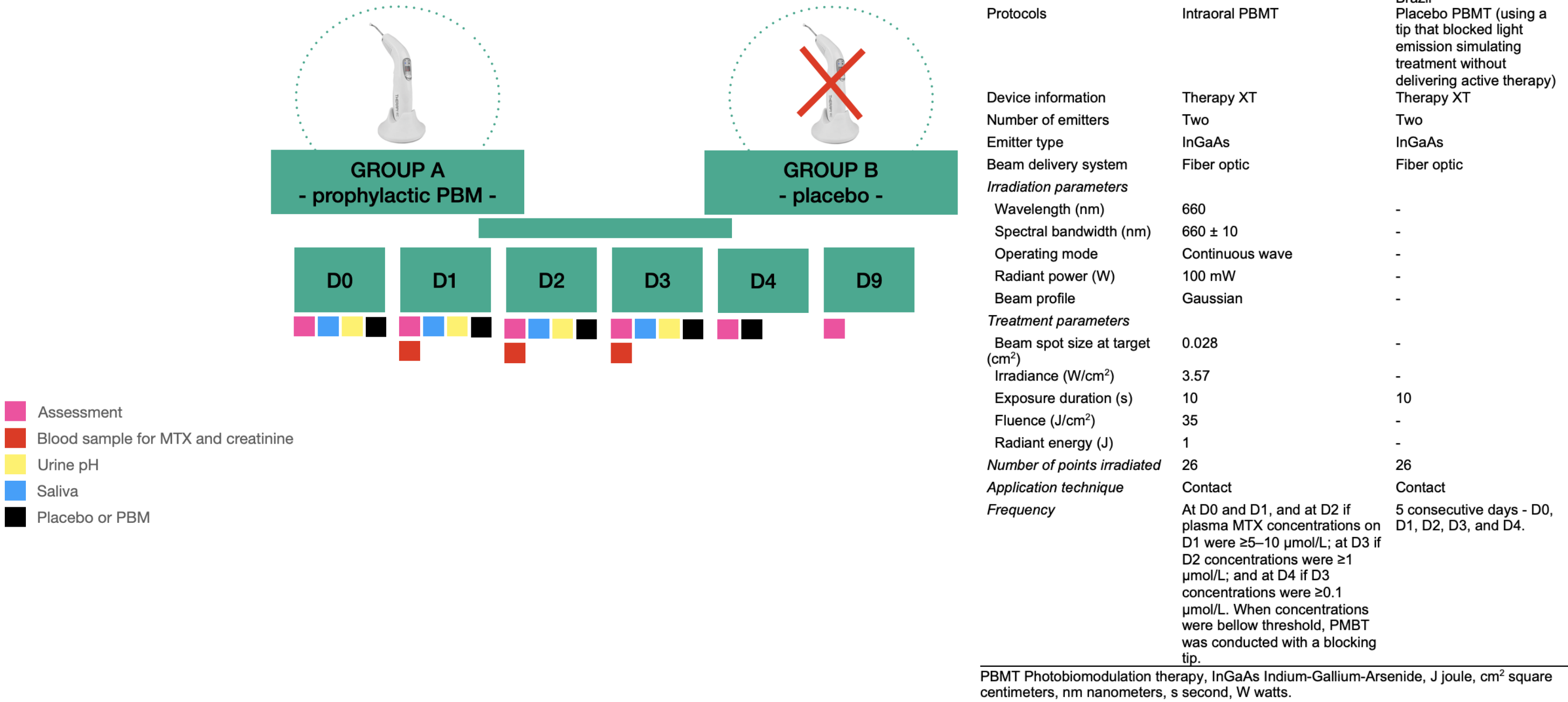


Table 1. Oral mucositis prevalence in Group A and group B, odds ratio, and relative risk.

OM	0	1	2	3	OR (CI 95%)*	P* value
Group A	8 (30.77%)	14 (53.85%)	4 (15.38%)	0 (0%)	ref	<0.01
Group B	1 (3.7%)	10 (37.04%)	14 (51.85%)	2 (7.41%)	8.97 (2.66; 30.22)	

OM	0 and 1	2 and 3	RR (CI 95%)**	P* value
Group A	22 (84.62%)	4 (15.38%)	ref	
Group B	11 (40.74%)	16 (59.26%)	3.85 (1.48; 10.0)	<0.01

Abbreviations. OM: oral mucositis. OR: odds ratio. CI: confidence interval. RR: relative risk.

A P-value less than 0.01 was considered significant.
* *multinomial logistic regression*
** *robust-error-variance Poisson regression analysis.*

Figure 1. Serum and salivary MTX concentrations at 24h, 48h, and 72h after HD-MTX infusions.

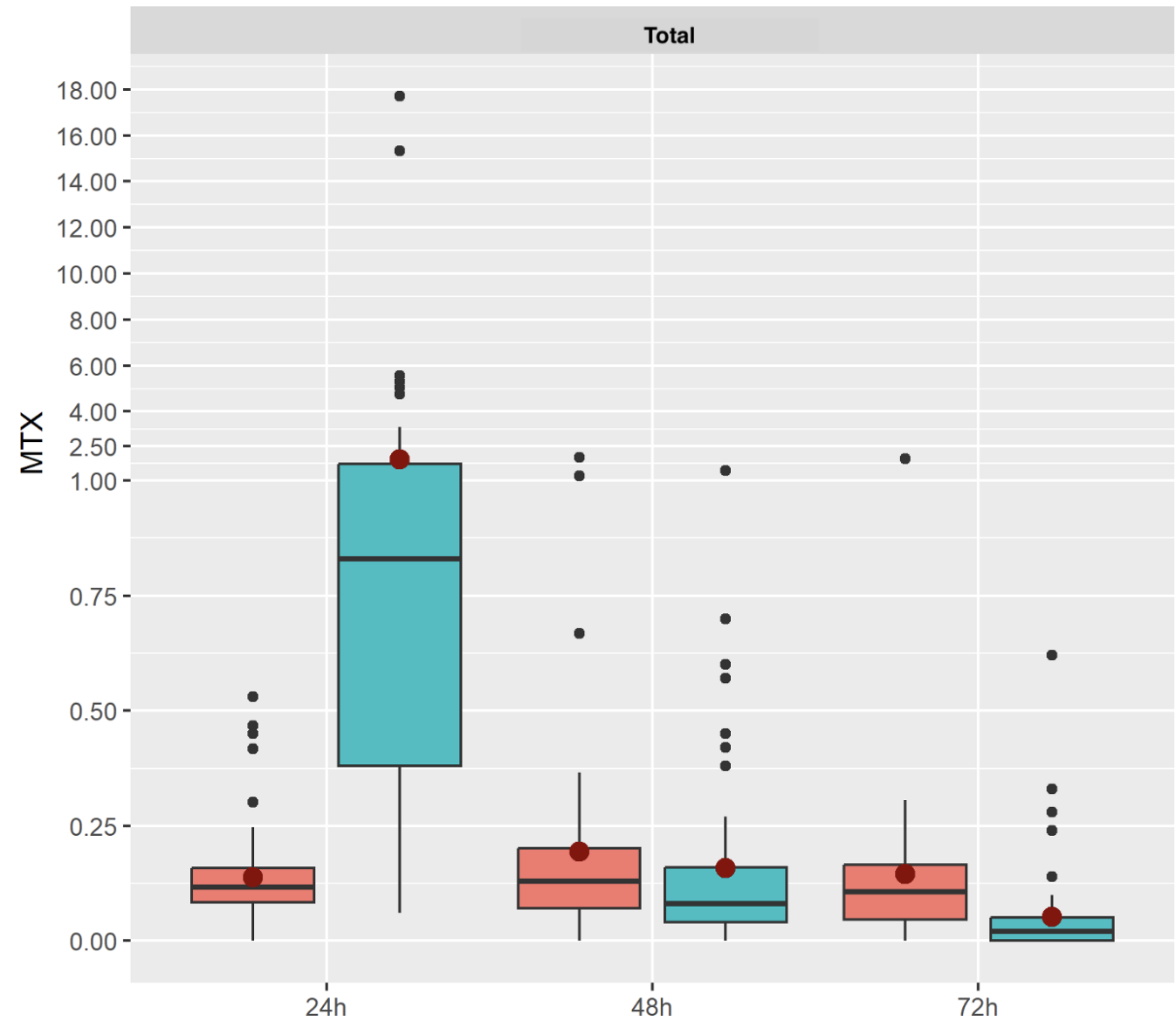
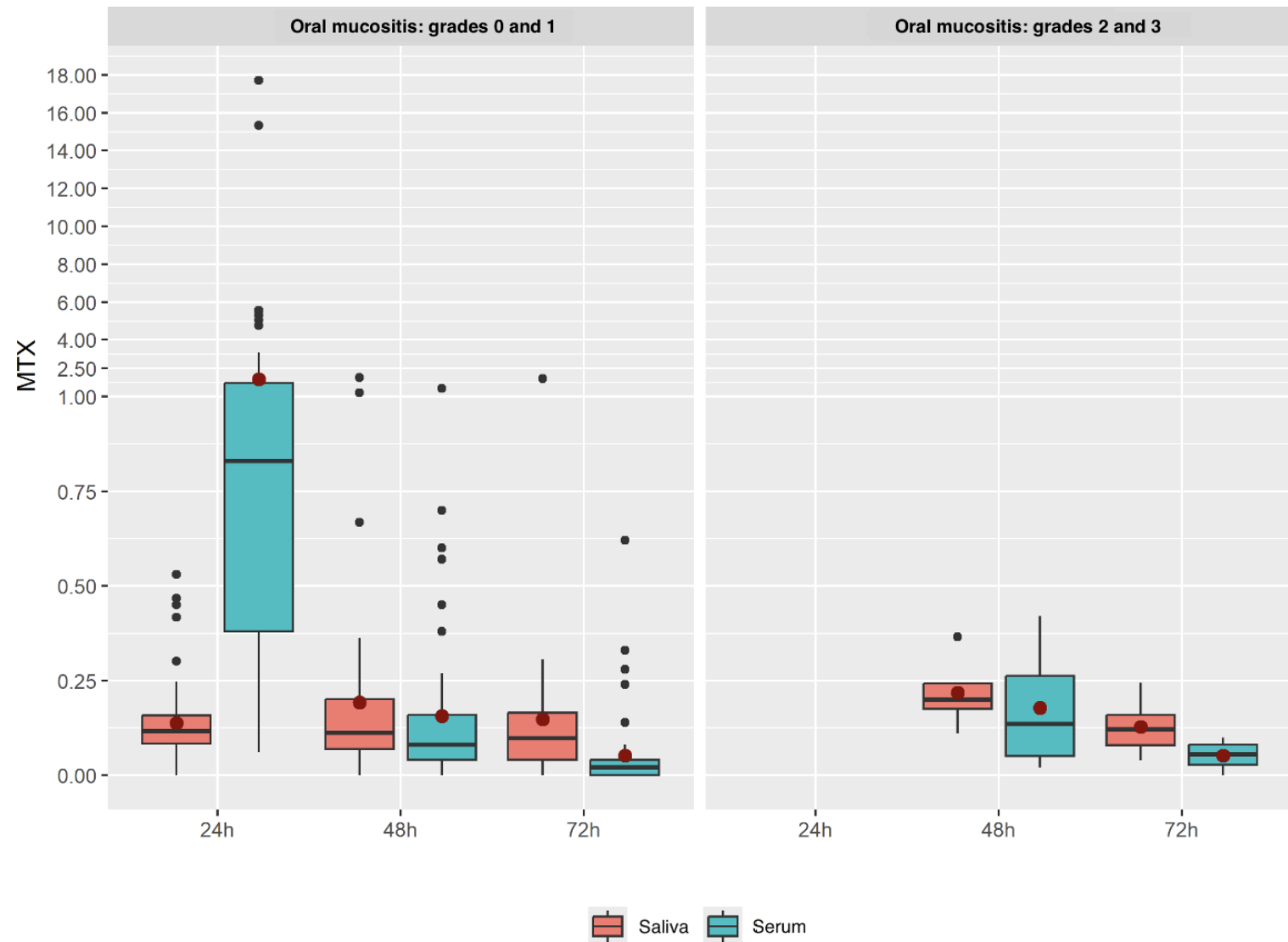


Figure 2. Oral mucositis grades 0 and 1, grades 2 and 3, and its correlation with serum and salivary MTX concentrations at 24h, 48h, and 72h.



CONCLUSIONS

PBMT effectively reduced the incidence and severity of OM in HD-MTX-treated patients. Additionally, salivary MTX excretion may serve as a predictive marker for OM in HD-MTX treatment protocols.

ACKNOWLEDGMENTS: The authors would like to CNPq/MCTI/FNDCT for its financial support through grant 56577059000606.

Joannon, P., Oviedo, I., Campbell, M., & Tordecilla, J. (2004). High-dose methotrexate therapy of childhood acute lymphoblastic leukemia: Lack of relation between serum methotrexate concentration and creatinine clearance. *Pediatric Blood and Cancer*, 43(1), 17–22. <https://doi.org/10.1002/pbc.20032>

Schrøder, H., Jensen, K. B., & Brandsborg, M. (1987). Lack of correlation between methotrexate concentrations in serum, saliva and sweat after 24 h methotrexate infusions. *British journal of clinical pharmacology*, 24(4), 537–541. <https://doi.org/10.1111/j.1365-2125.1987.tb03208.x>

Ishii, E., Yamada, S., Higuchi, S., Honjo, T., Igarashi, H., Kanemitsu, S., Kai, T., & Ueda, K. (1989). Oral mucositis and salivary methotrexate concentration in intermediate-dose methotrexate therapy for children with acute lymphoblastic leukemia. *Medical and pediatric oncology*, 17(5), 429–432. <https://doi.org/10.1002/mpo.2950170514>

44. Albertioni, F., Rask, C., Schroeder, H., & Peterson, C. (1997). Monitoring of methotrexate and 7-hydroxymethotrexate in saliva from children with acute lymphoblastic leukemia receiving high-dose consolidation treatment: relation to oral mucositis. *Anti-cancer drugs*, 8(2), 119–124. <https://doi.org/10.1097/00001813-199702000-00003>

Curra, M., Gabriel, A. F., Ferreira, M. B. C., Martins, M. A. T., Brunetto, A. T., Gregianin, L. J., & Martins, M. D. (2021). Incidence and risk factors for oral mucositis in pediatric patients receiving chemotherapy. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*, 29(11), 6243–6251. <https://doi.org/10.1007/s00520-021-06199-5>.

De Castro, J. F. L., Abreu, E. G. F., Correia, A. V. L., Da Mota Vasconcelos Brasil, C., Da Cruz Perez, D. E., & De Paula Ramos Pedrosa, F. (2013). Low-level laser in prevention and treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia. *Photomedicine and Laser Surgery*, 31(12), 613–618. <https://doi.org/10.1089/pho.2012.3327>