Methaemoglobinemia after Liposuction under Tumescent Local Anaesthesia – Diagnostic Value of Pulse Oximetry

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Received: 25 Jan 2021
Accepted: 05 Aug 2021

ABSTRACT

Background:
Tumescent local anaesthesia with prilocain can lead to clinically significant methemoglobin levels. New generation multiple wavelength pulse oximeters (e.g. Masimo Radical 7®) can measure methemoglobin levels.

Methods:
In this prospective observational study we compared the venous methemoglobin levels and the corresponding pulse oximetric values of the Radical 7® in patients undergoing tumescent local anaesthesia for liposuction procedures. The measurements were performed in Hanseklinik, Luebeck, Germany between 2008 and 2011.

Results:
In 133 patients, we measured a maximum methemoglobin level of 18 per cent. In a Bland-Altman analysis we found a mean bias of +2.2 % (-4.1 to 8.4 limits of agreement) for pulse oximetric values compared to hemoximetry.

Conclusion:
Pulse oximetric measurement of methemoglobin is an early-warning tool for the detection of clinically significant methaemoglobinemia in patients with tumescent local anaesthesia.

KEYWORDS
Tumescent anaesthesia, Methaemoglobinemia, Pulse oximetry, Liposuction

Please cite this paper as:
Brandt S., Kimberger O., Weber B., Klose A., Stockmann S., Schmeller W., Gehring H., Kellner P. Methaemoglobinemia after Liposuction under Tumescent Local Anaesthesia – Diagnostic Value of Pulse Oximetry. World J Plast Surg. 2022;11(1):111-116.
doi: 10.52547/wjps.11.1.111

INTRODUCTION

Tumescent anaesthesia is a local anaesthesia procedure, which is performed when plastic cosmetic surgical procedures such as liposuction are carried out. The subcutaneous adipose tissue is infiltrated with large volumes of a solution, which also contain local anaesthetics. Because of its low systemic toxicity, the local anaesthetic prilocaine is used in Europe amongst other agents. However, the use of prilocaine, like other local anaesthetics, can also lead to a marked production of methemoglobin. Methemoglobin (MetHb) is produced as a result of the oxidation of divalent iron to its trivalent form within haemoglobin (Fe²⁺ → Fe³⁺).
MetHb cannot bind or transport oxygen and is reduced by the enzyme MetHb reductase back to haemoglobin. A certain concentration of MetHb (0 to 1.5%) is also present under physiological conditions as a result of the auto-oxidation that naturally occurs within erythrocytes. While healthy people can tolerate higher concentrations of MetHb (up to about 30%) relatively well, patients with pre-existing anaemia and cardiopulmonary disease are subject to a higher risk. During a Medline search for preparing a review, Guay found 68 published case reports on prilocaine-induced methaemoglobinemia. The maximum published MetHb concentration in the blood was 42%.

The reference method for diagnosing methaemoglobinemia has been and remains direct measurement of MetHb in the blood using a hemoximeter, usually as a component of a blood gas analyser. A useful addition to this invasive and discontinuous measurement procedure would be a simple, non-invasive method for continuous MetHb monitoring. Conventional 2-wavelength pulse oximeters are not, however, able to diagnose methaemoglobinemia. Pulse oximeters, which measure the absorption in several wavelength ranges simultaneously, are able to determine pulse oximetrically the concentration of dyshaemoglobins such as MetHb.

The aim of this method-comparison study was to investigate multi-wavelength pulse oximetry as a monitoring method for patients at increased risk for methemoglobinemia.

**MATERIALS AND METHODS**

After approval by the Ethics Committee of the University of Luebeck, Luebeck, Germany and after patient information and acquisition of written informed consent, 133 patients scheduled for liposuction employing tumescent anaesthesia were included in the study. The study was conducted in 2008 up to 2011 as collaboration between the University Hospital Schleswig-Holstein and the Hanse Clinic in Luebeck. The study was registered on www.clinicaltrial.gov under NCT01766999.

Before surgery, all patients were subjected both to a venous blood gas analysis (GEM 4000, Instrumentation Laboratory, Bedford, MA, USA) and a pulse oximetry measurement using a multi-wavelength pulse oximeter (Radical-7, Masimo Corp., Irvine, CA, USA). During surgery, all patients were monitored continuously using a multi-wavelength pulse oximeter, which is able to measure MetHb (%SpMet). If there was an intra-operative increase in %SpMet to readings ≥ 8, further pulse oximetric and hemoximetric measurements were introduced after surgery and/or in the evening and the next morning. In such a case the pulse oximeter data was analysed continuously using a data acquisition program (Trendcom, Masimo Corp., Irvine, CA, USA). For detailed description see the flowchart (Figure 1).

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**Fig. 1: Experimental Protocol**

- **Preoperative**
  - 1st Timepoint: Venous Hemoxy; SpMet

- **During Liposuction**
  - 2nd Timepoint: Venous Hemoxy; SpMet

- **Postoperative**
  - 3rd Timepoint: Venous Hemoxy; SpMet

- **Evening / Next Morning**
  - No further Measurement: only 1st Timepoint into Analysis

- n=133
- n=72
- n=53
- n=44

* See Method Section for definition
The tumescent anaesthesia was introduced using a modified solution according to Schneider-Affeld and Friedrich, containing 30 ml prilocaine 2%, 30 ml lidocaine 2%, 2 ml epinephrine 1:1,000, 20 ml sodium bicarbonate 8.4%, triamcinolone 20 mg, and sodium chloride 0.9% made up to 3000 ml.

**Statistical analysis**

The pulse oximetrically and haemoximetrically obtained values for oxygen saturation (SpO₂ or SaO₂) and MetHb (%SpMet or MetHb%) were evaluated using Bland-Altman for repeated measurements analysis.

All analyses were performed using the software programs “R” and Prism 5.0 for Mac OS X (GraphPad Software, Inc., La Jolla, CA, USA).

**Error grid analysis**

In addition, we also prepared a so-called Error Grid in order to assess the clinical relevance of the deviations and to prepare graphs to illustrate them. Clarke et al. originally developed this method to test the reliability of blood glucose meters. Morey et al. proposed this method for globin measurement.

The error grid shows the absolute values of the new and the reference tests, as well as the clinical relevance of the deviation. For this purpose specific zones were initially defined by experienced clinicians. Clarke et al. defined 5 different zones. Since for MetHb there is no equivalent for hypoglycaemia, we restricted ourselves to the definition of 3 zones (A, B, C).

**Zone A (green)**

In zone A all measurement pairs are located for which:

1. The difference between the reference method (MetHb haemoximetrically in %) and the test procedure (% SpMet) is no more than ± 10%. In this case the accuracy of the new device can be considered as sufficient.

2. Both the reference and the test methods show values within the non-hazardous range of ≤ 10% MetHb. In this case, no further diagnostic or therapeutic decisions are affected.

3. Both the reference and the test methods show values within the hazardous range of ≥15 %. In this case, further diagnostics will always be applied (reference procedure!) and a therapeutic decision will have to be made that will be tailored for the individual case.

**Zone B (yellow)**

Zone B contains values where the test procedure reveals a significant error compared to the reference method, but the deviation is not as severe as it is with zone C.

**Zone C (red)**

Zone C includes pairs of measured values for which the error of the test method could lead to potentially dangerous erroneous decisions for the patients. Zone C is divided into two, with the lower right area containing measurements where the test procedure revealed non-hazardous %SpMet values of ≤ 10%, and the reference procedure revealed hazardous values of ≥ 15%. The upper right area of zone C contains measurement pairs where the test procedure revealed dangerously high %SpMet values of ≥ 15%, but the reference procedure reported levels of ≤ 10% in the safe range.

After the zones were defined, we modified a freely available script from the internet for the software package MATLAB Version 7.6.0 (The MathWorks Inc., Natick, MA, USA) and adapted it to our needs.

**RESULTS**

**Methemoglobin values**

A total of 133 female patients were included in the study. Details of the patients and the surgery performed can be found in Table 1. We found no correlation between maximum MetHb value and infiltrated TLA solution volume. No serious methaemoglobinemia-related complications occurred in the study population. No patient received any antidote.

The highest MetHb value measured by hemoximetry was 18.0% (corresponding %SpMet 28.2%), the highest measured %SpMet value was 36.6% (corresponding MetHb 14.1%) (Table 2).

| Variable          | Mean ± SD             |
|-------------------|-----------------------|
| Body weight       | 85 ± 19 kg            |
| Infiltrated fluids| 7919 ± 2062 ml        |
| Infiltrated prilocaine | 30.8 ± 8 mg       |
| Aspirated fluids  | 1292 ± 866 ml         |
| Aspirated lipids  | 3169 ± 2531 ml        |
| Liposuction time  | 82 ± 18 min           |

Table 1: Demographic Values
%SpMet\(^*\) for the diagnosis of methaemoglobinemia

In 61 patients, pulse oximetry revealed a %SpMet\(^*\) of ≥ 8% postoperatively, which according to the study protocol triggered further measurements. Between haemoximetrically measured MetHb concentrations and %SpMet\(^*\) we observed a mean bias of +2.2% (-4.1 to 8.4, 95% limits of agreement; n=286) using the Bland-Altman analysis for repeated measurements (Figure 2). Lin’s Concordance Correlation Coefficient between MetHb and %SpMet\(^*\) was 0.79 (0.73 to 0.84 confidence level).

Furthermore, we also calculated the sensitivity and specificity for the pulse oximetric determination of %SpMet\(^*\). For the cut-off value a MetHb level of ≥ 8% was selected, which we considered to be the threshold for a clinically relevant methaemoglobinemia. For %SpMet\(^*\) a sensitivity of 1.0 and a specificity of 0.45 was calculated (MetHb ≥ 8%, for details see Table 3). As demonstrated in Figure 3 the error-grid analysis yields to the following distribution of measurement pairs: Zone “A” 61 % (n=175); Zone “B” 39 % (n=110) and in Zone “C” 0.3 % (n=1).

DISCUSSION

Using a prilocaine containing tumescence anaesthetic solution for liposuction a clinically relevant methaemoglobinemia of > 8% was induced in 23% of our study patients. The development of methaemoglobinemia in an individual patient with tumescent anaesthesia cannot be predicted. In our patient population we found no correlation between infiltrated TLA solution and maximum MetHb. Responsible for this variability could be the existence of genetic variants for methemoglobin reductase 17. In addition, a glucose-6-phosphate dehydrogenase deficiency in the patient might also have been responsible for a delayed MetHb reduction. Mang et al. reported maximum MetHb levels 12 hours post infiltration and a correlation with the TLA solution amount 18. This phenomenon of “late onset” methaemoglobinemia in some patients is already known. It should always be considered when tumescence anesthesias are being carried out. Although methemoglobin levels of up to 15% are

| Time point          | pH     | BE (mmol·L\(^{-1}\)) | Lactate (mmol·L\(^{-1}\)) | MetHb (%) | tHb (g·dl\(^{-1}\)) |
|---------------------|--------|----------------------|---------------------------|-----------|---------------------|
| Preoperative n = 133| 7.35 ± 0.05 | -1.2 ± 1.8          | 1.8 ± 0.6                  | 0.4 ± 0.3  | 14.1 ± 1.0          |
| Postoperative n = 41| 7.31 ± 0.05 | -8.5 ± 9.4          | 3.0 ± 1.0                  | 8.5 ± 2.7  | 12.7 ± 1.0          |
| Evening n = 50      | 7.35 ± 0.04 | -5.9 ± 2.5          | 2.5 ± 0.8                  | 8.2 ± 3.4  | 12.1 ± 0.9          |
| Next morning n = 57 | 7.39 ± 0.03 | -3.2 ± 1.8          | 1.6 ± 0.8                  | 5.5 ± 3.0  | 11.7 ± 0.9          |
generally well tolerated in healthy individuals, risk patients (e.g. patients with anaemia or pre-existing cardiopulmonary conditions) can show clinical symptoms already from a level of 8% MetHb. For such patients in particular an early diagnosis is necessary to avoid complications due to the reduced oxygen-carrying capacity of the blood arising from the elevated methemoglobin. For this purpose pulse oximetric measurement of %SpMet® appears to be an appropriate monitoring procedure from our perspective. Although a clinically relevant methaemoglobinemia (≥ 8%) is detected with a sensitivity of 100%, the specificity of pulse oximetry at 45% is markedly inferior. The manufacturer states that the accuracy of SpMet% in subjects with a MetHb range of 1-15% ± 1% is comparable to that of a hemoximeter. Feiner et al. showed that the Masimo Rainbow SET Radical 7 pulse CO-oximeter reports falsely high %SpMet® values in hypoxemic subjects. After introducing an improved firmware version, the same group reported an acceptable accuracy in the SaO₂ range of 74% - 100% and with MetHb levels of 0% - 14%. However both studies were performed under controlled experimental conditions in volunteers.

Our results indicate firstly that the tested multi-wavelength pulse oximeter systematically overestimates the MetHb possibly in order to avoid the reporting of false-negative results. For a monitoring procedure this is certainly quite reasonable. In clinical practice this would mean that after measurement of a clinically relevant high %SpMet® value a blood sampling would have to follow to confirm the diagnosis of a methaemoglobinemia. If the %SpMet® shows no high values, a methaemoglobinemia can be excluded for that time-point.

One limitation of our study is that we measured methemoglobin haemoximetrically in venous blood, while for pulse oximetry arterial blood was used. This could theoretically be responsible for a portion of the bias observed. In an earlier study, our group showed in 276 blood samples that the difference between with arterial (2.16 ± 1.48 %; mean ± SD) and venous MetHb (2.00 ± 1,34 %) is small. The fitting of an arterial catheter for a period of up to 24 hours could not be ethically justified for a liposuction intervention.

Another limitation is that it is possible that the measurement accuracy of the Radical7® changed as a result of the introduction of newer firmware versions since we carried out our study. The results of the work of Feiner et al. might also indicate that the measurement accuracy has been improved somewhat.

CONCLUSION

The use of a multi-wavelength pulse oximeter for patients undergoing surgical procedures in TLA can be justified not only in the low MetHb range up until 6.7% MetHb, but also at higher, clinically relevant MetHb levels. However in the tested configuration it should be used as a methemoglobin early-warning system rather than as a measurement device.

ACKNOWLEDGMENTS

Results of this study have been presented in parts as a poster at the ASA 2010 annual...
meeting, October 2010, San Diego, CA, USA. Dr. Brandt has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no 238802 (IIIOS project). The blood gas analyser and the multi wavelength pulse oximeter were items on loan of the manufacturers.

CONFLICT OF INTEREST

Non-declared.

REFERENCES

1. Scott D, Owen J, Richmond J. Methaemoglobinaemia due to prilocaine. Lancet 1964; 2: 728-729.
2. Wright R, Lewander W, Woolf A. Methemoglobinemia: Etiology, pharmacology, and clinical management. Ann Emerg Med 1999; 34: 646-656.
3. Guay J. Methemoglobinemia related to local anesthetics: A summary of 242 episodes. Anesth Analg 2009; 108: 837-845.
4. Barker S, Tremper K, Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. Anaesthesiology 1989; 70: 112-117.
5. Reynolds K, Palayiwa E, Moyle J, Sykes M, Hahn C. The effect of dyes on methemoglobinemia on pulse oximetry and mixed venous oximetry. J Clin Monitor 1993; 9: 81-90.
6. Yang J, Lin N, Lv R, Sun J, Zhao F, Zhang J, Xu J. Methemoglobinemia misdiagnosed as ruptured ectopic pregnancy. Acta Anaesthesiologica Scandinavica 2005; 49: 586-588.
7. Feiner J, Bickler P, Mannheimer P. Accuracy of methemoglobin detection by pulse oximetry during hypoxia. Anesth Analg 2010; 111: 143-148.
8. Soeding P, Deppe M, Gehring H. Pulse-oximetric measurement of prilocaine-induced methemoglobinemia in regional anesthesia. Anesth Analg 2010; 111: 1065-1068.
9. Schmeller W, Meier-Vollrath I. Zum aktuellen Stand der Liposuktion. Der Deutsche Dermatol 2002; 9: 590-594.
10. Bland J, Altman D. Stat Methods Med Res 1999; 8: 135-160.
11. Bland J, Altman D. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat 2007; 17: 571-582.
12. R. The R Project for statistical calculations. In: http://www.r-project.org (4th Dec 2020).
13. Clarke W, Cox D, Gonder-Frederick LA, Carter W, Pohl S. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care 1987; 10: 622-628.
14. Morey T, Gravenstein N, Rice M. Assessing point-of-care hemoglobin measurement: Be careful we don’t bias with bias. Anesth Analg 2011; 113: 1289-1291.
15. Morey T, Gravenstein N, Rice M. Let’s think clinically instead of mathematically about device accuracy. Anesth Analg 2011; 113: 89-91.
16. Codina EG. Clark Error Grid Analysis. In: http://www.mathworks.com/matlabcentral/fileexchange/20545-clark-error-grid-analysis (27 July 2020).
17. Jaffe E. Enzymopenic hereditary methemoglobinemia: A clinical/biochemical classification. Blood Cells, Molecules and Diseases 1986; 12: 81-90.
18. Mang W, Materak J, Kuntz S, Sawatzki K, Arnold W. Liposuction in tumescent local anaesthesia: Maximum recommended doses for prilocaine. Zeitschrift für Hautkrankheiten 1999; 74: 157-161.
19. Ash-Bernal R, Wise R, Wright S. Acquired methemoglobinemia: A retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore) 2004; 83: 265-273.
20. Feiner J, Bickler P. Improved accuracy of methemoglobin detection by pulse co-oximetry during hypoxia. Anesth Analg 2010; 111: 1160-1167.
21. Deppe M. Pulsoximetricisches Monitoring von Methämoglobin bei Regionalanästhesien mit Prilocain. Doctoral Thesis, University of Luebeck, Faculty of Medicine 2009; 1-80.