Perioperative Outcomes of Hyperlactatemia during Craniotomy: A Systematic Review and Meta-Analysis of 1,832 Patients

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Abstract

Background Hyperlactatemia, is common in patients undergoing neurosurgical procedures. Several studies have identified potential risk factors for developing hyperlactatemia in neurosurgical patients, including body mass index, surgery duration, tumour volume, and certain drugs such as volatile anesthetic agents and corticosteroids. This systematic review and meta-analysis examined the evidence of the association between perioperative lactate levels in patients undergoing brain surgery and postoperative morbidity and mortality.

Methods Using PubMed, Scopus, Web of Science, Embase, CINAHL, Medline, Google Scholar, and the Cochrane Central Register of Controlled Trials databases, a systematic literature search was conducted for studies examining the association between perioperative hyperlactatemia and postoperative outcomes in patients undergoing brain surgery. Two authors independently evaluated the full-text papers for eligibility, and then data extraction and meta-analyses of similar studies were conducted (using a random effect model for each outcome measure). The Newcastle Ottawa Scale was used to evaluate the risk of bias (NOS scale).

Results Seven observational studies were included, and a total of 1,832 patients were assessed in the systematic review and meta-analysis. The quality of the included studies ranged from poor to high quality according to the NOS quality assessment tool. Meta-analysis results revealed no significant association between perioperative hyperlactatemia and postoperative new neurological deficits (five studies; odds ratio [OR] = 0.97, 95% confidence interval [CI] 0.50–1.87, p = 0.92; heterogeneity: I² = 38%, p = 0.18). Similarly, perioperative hyperlactatemia was neither significantly associated with increased 30-day postoperative mortality (two studies; OR = 0.20, 95% CI [0.02–
Introduction

A high mortality rate is associated with lactic acidosis (type A hyperlactatemia).7 Hyperlactatemia type B, or increased serum lactate without acidosis, is a condition with poorly understood underlying causes and prognosis.8 Contrary to type A, type B hyperlactatemia is unrelated to hypoxia or inadequate perfusion of tissues.9 Hyperlactatemia of type B is quite prevalent among patients undergoing neurosurgery; however, it is unknown whether or not this condition influences the outcome in neurosurgical patients, with a prevalence of up to 67% of patients following brain tumour resection.4–6 Additionally, there are several explanations for why hyperlactatemia develops in patients undergoing craniotomies.

Hyperlactatemia is always linked to hypoperfusion, but not during neurosurgical procedures.7 Lactate is generated from pyruvate in the glycolysis pathway. Normal aerobic conditions produce and metabolize lactate continuously. In low or interrupted oxygen, anaerobic metabolism increases serum lactate.7 During craniotomies, systemic hypoperfusion from volume under resuscitation or concomitant medical issues (such as congestive heart failure) can cause high blood lactate.1 A high lactate level has been considered an early sign of cerebral hypoperfusion.17,18 The surgeon can utilize this data to search for correctable reasons like retraction or clips, and the anesthesiologist can use it to increase cerebral perfusion. Meanwhile, higher lactate levels might arise from preoperative dehydration, intraoperative hypothermia, and surgical complexity.6

Prolonged surgical time increases blood lactate levels,5,11 as prolonged immobility during anesthesia may explain this.19 Studies linking tumour growth to serum lactate levels have produced contradictory results.5,11,15 Some authors suggest that lactate acts as a biomarker for glioblastoma progression and therapeutic response,5 but others have not verified this.15 A high BMI may contribute to higher lactate levels.20 Hyperlactatemia is caused by muscle ischemia and tissue disintegration, and a high BMI worsens the problem. The elevated blood lactate levels in obese people may result from insulin resistance, a side effect of weight gain.21

The objective of this study is to review the relevant literature regarding the clinical significance of hyperlactatemia in patients undergoing brain surgeries; this would help clinicians determine whether elevated serum lactate can predict outcomes and thus guide the management.

Methods

The study protocol has been registered with the international prospective register of systematic reviews (PROSPERO identifier: CRD42022354030). We followed the most recent version of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement 2020) guidelines during the preparation of this article.22

Inclusion Criteria

Studies satisfying the following criteria were included in this systematic review and meta-analysis:

Population: Adult patients scheduled for craniotomy, either elective or emergency, for any brain space-occupying lesion or any neurovascular system lesion, neuroendocrine system lesion, or dural-meningeal system.

Control group: Craniotomy patients with normal lactate perioperatively (normal lactate).

Experimental group: Craniotomy patients with high lactate perioperatively (hyperlactatemia).

Outcomes:

Primary outcome: New postoperative neurological deficit.

Secondary outcomes: Thirty days mortality rate, length of hospital stay, and survival at 6 months.

Study design: Studies with comparative designs compare the outcomes of normal and elevated lactate levels, either randomized controlled trials or observational studies.

Exclusion Criteria

Studies that included patients with comorbid conditions that might cause increased lactate levels, including pre-existing severe liver or kidney disease and sepsis, were excluded.

Information Sources

We comprehensively searched these electronic databases PubMed, Scopus, Web of Science, Embase, CINAHL, Medline, Google Scholar, and Cochrane Central Register of Controlled Trials from inception to June 2022.
Search Strategy
We used the following search query (hyperlactatemia OR “High Lactate level” AND “Brain surgery” OR “Brain tumour resection” OR “Intracranial tumours resection” OR “Intracranial tumours Surgery” OR “Craniotomy” OR “Craniectomy”) in the seven databases with no filters or limitations.

Selection Process
Retrieved records from the literature search were screened in two steps manner. In the first step, the title and abstracts of all articles were screened for eligibility. Then, the full-text articles of the eligible abstracts were conducted for the reliability of data for meta-analysis and its eligibility for the systematic review. Two independent authors did the screening, and a third solved the disagreement.

Data Collection Process and Data Items
Data were extracted to a uniform data extraction sheet. The extracted data included (1) characteristics of the population of included studies, (2) characteristics of the included studies, (3) risk of bias domains, and (4) outcome measures.

Assessment of Risk of Bias
Two independent authors did the risk of bias assessment, and the disagreements were resolved by consensus. As all included studies in this review were observational studies, we used the Newcastle Ottawa Scale (NOS scale) for their assessment.23

Data Synthesis and Statistical Analysis
For continuous data, the mean difference (MD) between the two groups from the baseline to endpoint, with its standard deviation, and the total number of patients in each group were pooled as the odds ratio (OR) between the two groups from the baseline to endpoint, with its standard error in the pooled estimate, making it suitable for controversial or inconsistent estimates. The heterogeneity of the included studies was examined by visual inspection of the forest plots and assessed by the Cochrane Q and I² tests using RevMan version 5.3 for Windows. For heterogeneity testing, a p-value < 0.1 and an I² > 50% were considered for significant heterogeneity.

Results

Literature Search Results
Our search yielded 1,171 citations. Of these, 540 citations were retrieved and screened for title and abstract eligibility after duplicates were removed (n = 631) and irrelevant studies were excluded (n = 520). Twenty full-text articles were screened for eligibility, and seven studies (n = 1,832 patients) were included in our systematic review and meta-analysis4–6,11,15,17,18 (see the PRISMA flow diagram in Fig. 1).

Study Characteristics
A summary of the design and main findings of included studies is given in Table 1, and the baseline characteristics of their populations are displayed in Table 2.

Quality Assessment
All included studies showed good quality except Yoshikawa et al. This was fair due to the exposed cohort’s lack of representativeness and no demonstration that the outcome of interest was not present at the start of the study ( Fig. 2). The details of each domain are presented in Supplementary Table S1 (available in the online version).

Outcomes

Primary Outcome
Development of new neurological deficit
Five comparative studies4,6,11,17,18 were included, 716 normal and 608 elevated serum lactate patients. The odds of having new neurological deficits after lactate elevation was insignificant compared to the normal lactate (OR = 0.97, 95% confidence interval [CI] [0.50–1.87], p = 0.92). There was a significant heterogeneity (I² = 62%, p = 0.03), and after excluding Fazili et al, no heterogeneity (I² = 38%, p = 0.18) was present, but the overall OR still did not favor either of the two groups concerning this outcome (OR = 0.74, 95% CI [0.42–1.30], p = 0.29) ( Fig. 3).

Secondary Outcomes
1. Duration of hospitalization
Four comparative studies4–6,18 were included, 593 patients with normal lactate and 644 with elevated serum lactate...
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Title</th>
<th>Study design</th>
<th>Outcomes measured</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Smedt et al 2019$^1$</td>
<td>Hyperlactatemia after intracranial tumour surgery does not decrease survival during perioperative care series</td>
<td>Retrospective cohort study</td>
<td>Six-month survival, neurological condition after surgery, The need for rehabilitation</td>
<td>No associations were shown between hyperlactatemia and the development of new postoperative neurological complications, renal failure, myocardial infarction, or death within 30 days of surgery. The length of stay in the hospital was not significantly related to hyperlactatemia.</td>
</tr>
<tr>
<td>Romano et al 2020$^4$</td>
<td>Hyperlactemia after intracranial tumor surgery is not associated with length of hospital stay</td>
<td>Cohort study</td>
<td>Length of hospital stay, reason for admission, hospital discharge</td>
<td>No association between hospital stay and hyperlactatemia. Moreover, it was not significantly related to most postoperative new complications.</td>
</tr>
<tr>
<td>Kohli-Seth et al 2012$^6$</td>
<td>Clinical impact of intraoperative hyperlactatemia during craniotomy</td>
<td>Cohort study</td>
<td>Maximum lactate, serum lactate levels</td>
<td>In craniotomy patients, intraoperative hyperlactatemia was common after surgery. Results showed no significant association with any postoperative outcomes.</td>
</tr>
<tr>
<td>Cata et al 2017$^10$</td>
<td>Correlation between intraoperative serum lactate and new-onset postoperative neurological deficits</td>
<td>Retrospective study</td>
<td>Serum lactate levels</td>
<td>Elevated intraoperative serum lactate level was not a predictor of survival after elective craniotomy and was associated with new neurological deficits and longer length of stay.</td>
</tr>
<tr>
<td>Brallier et al 2018$^11$</td>
<td>Early postoperative hyperlactatemia in neurosurgical patients: a retrospective study</td>
<td>Retrospective study</td>
<td>Serum lactate levels</td>
<td>Early postoperative hyperlactatemia was detected in neurosurgical patients and was associated with worse neurological outcomes and longer hospital stay.</td>
</tr>
<tr>
<td>Fazili et al 2021$^17$</td>
<td>Intraoperative serum lactate is not a predictor of survival after craniotomy and longer length of stay</td>
<td>Cohort study</td>
<td>Serum lactate levels</td>
<td>No association between intraoperative lactate levels and survival or length of stay in the hospital.</td>
</tr>
<tr>
<td>Study ID</td>
<td>Groups</td>
<td>Sample size</td>
<td>Age (y)</td>
<td>Sex, male n (%)</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td>de Smalen et al 2020</td>
<td>Normal lactate</td>
<td>239</td>
<td>59.3</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>257</td>
<td>58.8</td>
<td>NR</td>
</tr>
<tr>
<td>Romano et al 2019</td>
<td>Normal lactate</td>
<td>55</td>
<td>51.6</td>
<td>(13.6)</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>26</td>
<td>48.5</td>
<td>(14.9)</td>
</tr>
<tr>
<td>Fazili et al 2021</td>
<td>Normal lactate</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cata et al 2017</td>
<td>Normal lactate</td>
<td>134</td>
<td>58 (49–66)</td>
<td>175 (68)</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>141</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Brallier et al 2017</td>
<td>Normal lactate</td>
<td>205</td>
<td>55.5 (15.1)</td>
<td>27.83 (7.3)</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>231</td>
<td>52.4 (15.6)</td>
<td>28.26 (6.5)</td>
</tr>
<tr>
<td>Yoshikawa et al 2018</td>
<td>Normal lactate</td>
<td>176</td>
<td>62 (15)</td>
<td>95 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>49</td>
<td>58 (15)</td>
<td>26 (5.3)</td>
</tr>
<tr>
<td>Kohli-Seth et al 2012</td>
<td>Normal lactate</td>
<td>94</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Elevated lactate</td>
<td>130</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IQR, interquartile range; IV, intravenous; NR, not reported; SD, standard deviation.

*Median (IQR).*
levels. There was no difference in the length of hospital stay between the two groups (MD = -0.85, 95% CI [-1.73 to 0.03], \(p = 0.06\)). Pooled studies were not homogenous (\(I^2 = 68\%\), \(p = 0.03\)), and the leave-one-out test did not resolve it (\(\text{Fig. 4}\)).

2. Mortality at 30 days

Brallier et al and Romano et al included a collective total of 517 patients, 260 with normal lactate and 257 with elevated lactate, and both studies reported a 30-day postoperative mortality rate. There was no difference between the two groups (OR = 0.20, 95% CI [0.02–2.00], \(p = 0.17\)), and pooled studies were homogenous (\(I^2 = 0\%\), \(p = 0.59\)) (\(\text{Fig. 4}\)). Thirty-day mortality was also comparable in both groups (0.4 and 1.6% for normal and elevated lactate, respectively).

3. Survival at 6 months

Three comparative studies included 467 normal and 528 elevated serum lactate patients. No significant differences were observed regarding the 6-month survival rate between the normal and elevated lactate groups (OR = 1.05, 95% CI [0.75–1.47], \(p = 0.79\)). Pooled studies were homogenous (\(I^2 = 0\%\), \(p = 0.51\)) (\(\text{Supplementary Fig. S2}\), available in the online version).

**Discussion**

**Summary of the Outcomes**

Our analysis included four comparisons with 1,832 individuals divided into two groups, high lactate levels versus normal lactate levels for patients who underwent craniotomy for different brain procedures. There was no significant difference between the two groups in the incidence of new neurological deficits postoperatively, the 30-day mortality rate, the survival at 6 months, and the hospital length of stay.

**Explanation of the Outcomes**

Lactate has been used as a guide for fluid resuscitation; however, studies show that too much fluid following general anesthesia might be harmful. Brallier et al found that hyperlactatemia patients given liters of crystalloids showed neurological impairments postoperatively. It has been claimed that stricter fluid management for hyperlactatemia, especially in neurosurgical patients, may improve patient safety and reduce difficulties and expenses.

The pooled analysis found no difference in postoperative neurological impairments. Only Brallier et al documented additional neurological impairments postoperatively among the five studies included in this outcome. However, this was a retrospective study, and the same team who conducted this study conducted another prospective study, Romano et al. Compared to a retrospective review, the outcomes of prospective screening for new neurologic impairments utilizing these criteria may vary and yield different results as neurologic status was evaluated in more detail than in the previous retrospective analysis. Also, evaluations were taking place at
regular intervals and utilizing a set of common impairments that neurosurgeons had defined in Romano et al.6

Romano et al15 focused solely on elective craniotomies when recruiting patients, whereas Brallier et al18 may have included inpatients, emergency surgeries, and patients with altered mental status. Patients who did not have their lactate levels collected were much healthier in a sensitivity analysis conducted in the retrospective study by Romano et al.6 Because these were elective outpatient craniotomies, it is possible that the anesthesiologists performing the procedures did not do arterial blood gas analyses (ABGs) on the patients intraoperatively, meaning that many of these individuals were left out of the prior study. This suggests that the two studies had distinct study populations, which could explain the discrepancy in detecting new neurologic deficits.6

A study by Fazili et al.17 reported a higher incidence of new neurodeficits postoperatively in patients with normal lactate compared to higher lactate; this may be attributed to the large variety of complex pathologies that patients had. They hypothesized that elevated serum lactate levels in individuals undergoing craniotomies occurred due to localized metabolic shifts or direct brain compression. Consistent with these results, de Smalen et al4 and Kohli-Seth et al5 found that postoperative hyperlactatemia is common in neurosurgical patients but seems benign and unrelated to mortality.

Patients with hyperlactatemia had hospitalization days comparable to those with normal lactate levels.4,6,18 Romano et al.6 in their prospective analysis, reported that the underlying mechanisms of prolonged hospital stay among hyperlactatemia patients are unclear. Consequently, some postoperative factors like infection, deep vein thrombosis, subclinical cerebral ischemia, or other factors could be measured in future studies to validate or better explain this association. As per Brallier et al.18 in their retrospective analysis, it is unclear whether the prolonged hospitalization is due to hyperlactatemia or its treatment.

On the other hand, recently conducted research has shown that lactate, a substrate for oxidation, can play a neuroprotective role. Hypertonic sodium lactate can moderate cerebral metabolism,25 which may reduce brain damage following trauma. Although this data is controversial,26 the possibility that an intrinsic protective mechanism is triggered after iatrogenic brain injury is intriguing, like during a craniotomy. After brain injury, Rice et al27 found that infusing the animals with lactate significantly improved their cognitive abilities compared to saline infusion. The authors argue that this impact has clinical significance, suggesting that lactate may be a viable therapeutic alternative for patients with moderate brain injury.

Neither the 30-day mortality nor the 6-month survival rates vary significantly between the two groups. According to Kohli-Seth et al,5 individuals with hyperlactatemia showed no symptoms of systemic hypoxemia, hypoperfusion, or liver failure. They concluded that these patients should be characterized as having benign postoperative hyperlactatemia. Benign postoperative hyperlactatemia in patients recovering from neurosurgery procedures has no apparent cause.

**Significance of the Work**

This study expands the literature by providing evidence that perioperative hyperlactatemia is not linked with postoperative neurological deficits, death risk, 6-month survival rate, or hospital stay.

**Strengths and Limitations**

This study has several strengths (1) this is the first meta-analysis conducted on hyperlactatemia in neurosurgical patients; (2) all steps were strictly conducted in accordance with the PRISMA statement guidelines as well as the Cochrane Handbook of Systematic Reviews and Meta-analysis; (3) the literature search was rigorous and conducted on multiple databases to identify all relevant studies as possible; (4) the research question was supported by clear eligibility criteria; and (5) each step in the review was done by two reviewers to ensure accuracy. On the other hand, the major limitation of our meta-analysis is that all of the included studies are observational, which is known to be susceptible to confounding bias and unreliable in establishing a causal association between the intervention and the clinical outcome. In addition, the majority of included studies were retrospective, meaning that the collected data may not have matched the nature of the study, creating the possibility of bias.

**Conclusion**

During brain surgery, hyperlactatemia is frequent. Hyperlactatemia can be caused by systemic hypoperfusion or regional cerebral ischemia. Their management varies; therefore, it is essential to differentiate between both.
neurosurgical patients, hyperlactatemia has been associated with several risk factors, including high BMI and tumour volume. This meta-analysis of 1,832 neurosurgical patients having an intracranial procedure with high or normal serum lactate levels pointed out that hyperlactatemia is not associated with unfavorable outcomes.

Conflict of Interest
None declared.

References
13. Horn T, Klein J. Lactate levels in the brain are elevated upon exposure to volatile anesthetics: a microdialysis study. Neurochem Int 2010;57(08):940–947