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Systemic mastocytosis

Systemic onset juvenile idiopathic arthritis

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 13 | 2021

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

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OrphanAnesthesia –

a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

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Anaesthesia recommendations for

Systemic mastocytosis

Disease name: Systemic mastocytosis (SM)

ICD 10: C96.2

Synonyms: -

Disease summary:

a) Definition and types

Systemic mastocytosis (SM) results from clonal proliferation of abnormal, aberrant mast cells in various organs and tissues, with or without skin involvement [36,46]. It is characterised by symptoms that originate from mast cell-associated organ dysfunction or overactivity and thus an excessive release of numerous cellular mediators. The disease is notable for the large number and hyperactivation of mast cells. This may lead to a highly variable disease phenotype [39]. An acute release of mast cell mediators causing anaphylaxis is a sudden and life-threatening manifestation of the disease, especially during anaesthesia. Furthermore, SM leads to organ infiltration and acute and chronic release of mast cell mediators, which is occasionally a related clinical manifestation [17].

Since 2016, SM is no longer considered a subgroup of myeloproliferative neoplasms but constitutes a separate category according to WHO classification, which distinguishes five subtypes of SM: indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), SM with an associated haematological neoplasm (SM-AHN), and the mast cell leukaemia (MCL). ASM, SM-AHN and MCL are summarised as advanced SM. A disposition to allergic reactions is more frequently observed in patients with indolent subtypes compared to advanced SM, which underlines the significance of a correct initial diagnosis and classification. For detailed information referring to each subtype, we recommend checking the specific literature [1,33,39].

Beside the systemic form, the cutaneous form or cutaneous mastocytosis (CM) is limited to the skin and constitutes the most frequent type (90 %) of mastocytosis.

b) Pathophysiology

The origin of symptoms in SM result from overactivation of mast cells and consecutive excessive release of histamine, heparin, tryptase, acid hydrolases, leukotrienes, prostaglandins, platelet activating factor, interleukins and tumour necrosis factor [39]. In ISM, symptoms usually originate from the release of mast cell mediators, e.g. flush, allergic and anaphylactic reactions, while clinical features in advanced SM are more the consequence of mast cell infiltration with consecutive organ dysfunction, e.g. cytopenia, abnormal liver function, splenomegaly, malabsorption, rather than mast cell mediator release itself.

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In the aetiology of SM, most patients show activating, gain-of-function mutations in a transmembrane tyrosine kinase receptor for stem-cell factor (KIT) in their neoplastic mast cells. More than 80 % show a KIT D816V mutation, which stimulates uncontrolled mast cell proliferation and migration as well as their immortality. Additional, somatic mutations especially in advanced SM may have prognostic relevance [23].

c) Triggers

The following list shows some of peri-operative triggers, which may be relevant for the anaesthesia team:

Psychological factors: psychological or emotional stress, anxiety, sleep deprivation [14],

Temperature changes: hypo- or hyperthermia [14],

Mechanical factors: mechanical irritation, skin stimuli, tourniquet use, trauma, surgery itself (e.g. located in gastrointestinal tract due to a rich source of mast cells) [14,17],

Pharmacological factors: histamine-releasing benzylisoquinolines (e.g. atracurium, mivacurium) and nefopam are not recommended, furthermore rapid intravenous administration of histamine-releasing medication should be avoided whenever possible [14],

Other: pain, infections [14].

Mast cell activation may also occur spontaneously without an obvious trigger. Patients should also be provided with an emergency kit for self-administration containing an epinephrine pen to be used in case of anaphylaxis and awareness of disease exacerbation at any time [14,39].

d) Epidemiology (prevalence, age and sex distribution, inheritance pattern)

There are no precise data on the incidence or prevalence of SM. Due to the difficulty in recognising this disorder and its rarity, the incidence and prevalence of SM are likely to be underestimated. The incidence of advanced SM is significantly lower than that of ISM.

Depending on regions and population, the prevalence is estimated between 13:100,000 and 1:364,000 whereas its worldwide incidence is estimated to be 1:150,000. The prevalence in Europe is estimated to range between 1:7,700 and 1:10,400 [34]. Regarding Germany with 82 million inhabitants, a prevalence of at least 380 advanced SM cases is estimated [9,13,15,16,20,34,40,45,46].

SM preferentially affects Caucasians [34]. The gender distribution is approximately equal [7].

In children, 80 % of mastocytosis cases appear during the first year of life, and the majority is limited to the skin. Symptoms improve or resolve usually completely by adolescence. However, adults who develop mastocytosis more often have systemic forms of the disease, in which the individual disorders tend to persist. Less than 5 % of adult cases are limited to the skin only. But (mostly as urticaria pigmentosa) the skin of 80 % of the patients is chronically affected with ISM, the most frequent form in adulthood [45].

e) Clinical signs and symptoms

The clinical spectrum of SM is heterogeneous and ranges from a mild course with almost normal life expectancy in ISM to life-threatening organ involvement with a poor prognosis in advanced SM. Various organs may be involved and the degree and magnitude of affection of

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different organs may vary in each individual patient up to multiorgan dysfunction, shortened survival and death in advanced SM [36,48]. The table below gives an overview of the organs potentially affected and summarises the corresponding clinical symptoms [9,25,28,36,39,41,45]:

Skin:	pruritus, flushing, hives, angioedema
Gastrointestinal:	nausea, bloating, hyperacidity, vomiting, diarrhea, abdominal cramps, epigastric discomfort, gastroduodenal ulcer disease, ascites, hypersplenism, hepatomegaly, malabsorption or protein-losing enteropathy, weight loss
Cardiovascular:	collapse, syncope, dizziness, palpitations, heartburn
Respiratory:	dyspnea, wheezing, bronchospasm, infants: apneic spells and cyanosis
Central nervous system:	memory or cognitive difficulties, depression, headache, sleep disturbance, anxiety, mood changes; children: aggressive behavior
Musculoskeletal:	general constitution, generalised weakness, fatigue, arthralgias, myalgias, osteopenia, osteoporosis, back pain, bone pain
Immune system:	lymphadenopathy, splenomegaly, episodic anaphylactoid attacks)
Further symptoms:	sweats, chills, rhinorrhea

f) Diagnosis

Diagnosis of SM needs at least fulfilment of one major and one minor criterion or more than three minor criteria. Major criterion means microscopic detection of multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) in the bone marrow and/or other extracutaneous tissues. There are four supplementary minor criteria: a) >25 % of the mast cells (in biopsy of bone marrow or other extracutaneous organs) in the infiltrate are spindle-shaped or have atypical morphology, or (of all mast cells in bone marrow aspirate smears) >25 % are immature or atypical, b) detection of an activating point mutation at codon 816 of KIT in the bone marrow, blood or other extracutaneous organ, c) mast cells in bone marrow, blood or other extracutaneous organ express CD25 with/without CD2 in addition to normal mast cell markers, d) serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated myeloid neoplasm, in which case this parameter is not valid) [36].

g) Treatment

Up to now, SM is not curable. Treatment of SM is highly individualised and varies (especially in indolent subtypes) between observation and continued monitoring alone (for abnormal blood counts, end organ damage and disease progression) to symptom management (e.g. pruritus, diarrhea, vomiting), supportive measures (e.g. transfusion or osteoporosis treatment) to cytoreductive therapy (e.g. cladribine, hydroxyurea) for mast cell debulking in cases of advanced or treatment-refractory disease [36,39]. Advanced SM might be treated with tyrosine-kinase inhibitors (e.g. midostaurine, avapritinib). Allogenic stem-cell transplantation should be considered in eligible patients with aggressive disease or MCL [36,39].

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All SM patients and their medical staff should be aware of potential triggers of an SM exacerbation at any time and find strategies to avoid excessive mast cell activation in situations that may have caused release syndrome in the past [39]. Acute treatment of degranulation is recommended according to current guidelines for the treatment of anaphylaxis [32].

h) Prognosis

The prognosis of SM varies in each individual patient depending on the degree of systemic affection and organ failure. Usually, the median survival ranges between a few months and several years from the date of diagnosis in aggressive forms. The MCL carries the highest mortality of all subtypes. Moreover, life expectation may be even normal in indolent forms of SM [31,35,39]. Scoring systems are used for a better assessment of the patient's prognosis [24,35].

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

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Typical surgery

Depending on the kind of stimulus, the degree of degranulation may vary. Besides, unprovoked and spontaneous anaphylaxis is possible at every time during surgery and anaesthesia [9]. Any medical/interventional/surgical therapy (especially with pharmacological agents) might trigger acute degranulation with a broad spectrum of symptoms.

Frequent surgical procedures: biopsies in several tissues and organs (especially skin and bone marrow for detection of mast cell infiltration and at least diagnosis), (pathologic) fractures due to mast cell infiltration of bone marrow, osteoporosis and/or long-term steroid therapy.

Surgery with increased risk of mast cell mediator related symptoms and anaphylaxis: nearly every kind of surgery as well as diagnostic procedures with intravenous administration of radiocontrast media, major and especially gastrointestinal surgery might be more prone to mast cell degranulation (as these organs already physiologically contain high numbers of mast cells) [14,21].

Type of anaesthesia

Anaesthesia (as well as surgery) provides many non-pharmacological stressors (e.g. pain, medication, operative trauma, extreme changes in temperature), which may stimulate uncontrolled mast cell degranulation and hypersensitivity reaction up to cardiovascular collapse. Therefore, to avoid these triggers for mast cell release, the peri-operative management should be organised very carefully and with each participating discipline involved [16,18,22]. The individual patient's history might help in identifying such relevant stressors.

Nevertheless, a general recommendation regarding an ideal anaesthetic approach cannot be given, as there is an overall lack of data for anaesthesia in patients with SM. The general prevalence for anaphylaxis has been reported to be 22–49 % in adults with SM and 6–9 % in children [6,31]. In 18–25 % of the cases, drugs have been implicated as triggers for anaphylaxis in SM patients. However, hymenoptera venom is the most frequent trigger for anaphylaxis in SM [6]. Undergoing anaesthesia procedures, anaphylaxis occurs in about 0.4 % in adult patients with SM. Compared to this, the overall incidence of anaphylaxis or anaphylactoid reactions during anaesthesia in the general population is reported with 0.04–0.03 % [31]. Mediator-related symptoms occur with about 2 % slightly more frequent in adult SM patients [31].

In children, anaphylaxis and mediator-related symptoms arise in 2 % and 4 %, respectively. Major surgery, previous occurrence of anaphylaxis in the individual patient and general anaesthesia raise the frequency of anaphylaxis and mediator-related symptoms in SM patients. Furthermore, a prophylactic antimediator therapy (H1/H2 antihistamines, benzo-diazepines) given one hour before anaesthesia may lower the risk [31].

Therefore, peripheral regional anaesthesia techniques seem to be a safe alternative in patients with SM [21]. There is a report of urticarial reaction following a Bier's block and of mast cell degranulation at the end of a knee replacement after pre-operative femoral nerve block with ropivacaine. Other than the local anaesthetics used, ischaemia or tourniquet seemed to exert a relevant influence on SM exacerbation in both cases [5,38]. Furthermore, there are a few case reports on neuraxial (epidural) anaesthesia in patients with SM [22]. Despite a lack of data, a higher risk of anaphylactic reactions to local anaesthetics in patients with SM compared to the general population remains unlikely [3]. Although less amounts of

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potentially hazardous drugs need to be applied in case of regional/neuraxial anaesthesia, one should consider that an excellent stress and anxiety reduction is needed to shield affected patients and to avoid SM exacerbations due to stress, friction, tourniquets or extremes of temperature [48].

Thus, regional anaesthesia will be a feasible option for SM patients if an adequate control of potential stressors is achievable. Additionally, regional anaesthesia might be theoretically superior to general anaesthesia as fewer drugs will be needed (thus also reducing the risk for acute degranulation).

Medical procedures requiring (general or regional) anaesthesia are deemed potentially hazardous for patients with SM [21,46]. Anaesthetists and every member of the caregiver team should be aware of possible reactive or spontaneous episodic symptoms such as flushing, pruritus, bronchospasm and hypersensitivity reactions up to an anaphylactic shock at any time before, during or after anesthesia and surgery. Therefore, and because of the partially unpredictable risk factors as well as the degree of exacerbation in the individual patient, it is strongly recommended that patients with SM should be managed as high-risk cases [18,22,31,46].

However, SM should never be deemed as a contraindication for anaesthesia if adequate prophylaxis and management is performed and reasonable precautions are taken in advance.

Necessary additional pre-operative testing (beside standard care)

In principle, there are no evidence-based guidelines for the pre-operative prophylaxis of patients with SM [26]. Although there are insufficient (empirical) data that would support the usefulness of prophylactic antimediator therapy (H1-/H2-antihistamines, benzodiazepines), a large case series did not reveal any adverse effects when prophylaxis was given one hour before anaesthesia. Furthermore, in this case series, it decreased the probability of peri-operative symptoms associated with mediator release in SM patients and (although using the same anaesthetic drugs) some patients undergoing another anaesthetic procedure tolerated this better with pre-anaesthetic prophylaxis and implementation of an adequate sedation [31].

Anamnesis: A comprehensive evaluation of symptoms is recommended and triggers of mast cell activation symptoms should be exactly assessed and documented (e.g. heat, friction, anxiety, stress and drugs). Especially episodes requiring epinephrine are essential and should be particularly observed [39,48]. Nevertheless, there are a lot of case reports on patients undergoing many previous surgeries without any occurrences of adverse events before the first anaphylactic incident.

Basically, pre-procedure allergy or hypersensitivity testing, the measurement of specific IgE and skin tests for suspected allergens are not recommended for patients with SM on a routine basis. These tests may be performed with similar indications as they are in the general population and remain the gold standard for differential diagnosis of IgE-mediated incidence [16]. As SM is caused by non-IgE-mediated mechanisms, the test results do not exclude the occurrence of any (spontaneous) mast cell degranulation, e.g., due to psychological or physical stressors [16,21,26,46].

Many authors recommend testing the total serum tryptase under basal conditions in order to obtain an initial baseline value before beginning with the induction of anaesthesia and surgery. In acute reactions, and in order to facilitate the assessment of follow-up values, the total tryptase is considered to be a good marker for the current changes of mast cell burden

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[9,17,18,46]. The basal tryptase activity increases during anaphylaxis and returns to baseline level after 24 to 48 hours, whereas, mastocytosis must be ruled out if it persistently rises to ≥ 20 ng/mL [17].

Particular preparation for airway management

As far as is known, there are no anatomic peculiarities due to SM itself. Nevertheless, a standardised approach for airway examination and the detection of airway challenges is recommended. A thorough preparation for airway management should be based on the examination results.

For airway management, a laryngeal mask as well as an endotracheal tube have been used without problems in patients with SM [2,5,9,44].

Depending on the degree of abdominal involvement, a rapid sequence induction may be necessary. In this case, drugs with a higher risk for histamine release should be avoided in SM patients.

Especially because mast cell degranulation is barely predictable, does not peri-operatively occur consistently in each diagnosed patient and may arise spontaneously, a thorough preparation for emergency airway management should be anticipated at all times during medical attendance of affected patients [26]. Therefore, even for interventions planned in sedation (without invasive airway measures), a meticulous and well-prepared airway management is necessary with availability of the appropriate equipment due to possible severe bronchospasm or cardiorespiratory impairment [41].

Particular preparation for transfusion or administration of blood products

Patients with SM might display significant anaemia (due to bone marrow involvement, AHN, immunosuppressive or cytoreductive therapy) with appropriate recurring transfusions. Therefore, depending on scheduled surgery as well as the degree of anaemia, an adequate amount of blood products should be available.

Anaesthetists should consider that mast cell degranulation and consecutive heparin release may lead to haemorrhagic manifestations in patients with SM [48]. Furthermore, bone marrow involvement may cause thrombocytopenia, and hepatic fibrosis as well as intestinal lesions (with malabsorption of vitamin K) may be other reasons for haemorrhagic diathesis [28].

Particular preparation for anticoagulation

There are no specific recommendations for patients with SM.

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Particular precautions for positioning, transportation and mobilisation

Among different drugs and psychological stress, anaesthesiologists should pay attention to individual non-medical costimulatory initiators of mast cell degranulation including mechanical friction and pressure, physical exertion and thermal stress (both hot and cold) [25]. Special attention is recommended for positioning and the observance of pressure points in patients with SM, especially in cases of prolonged surgery and anaesthesia [9].

Due to possible osteopenia or severe osteoporosis in patients with SM, an appropriate positioning and manipulation should be aspired to avoid bone fractures [14].

The use of a tourniquet requires an exact interdisciplinary assessment and should be avoided whenever possible in patients with SM [5].

Interactions of chronic disease and anaesthesia medications

Long-term medication with corticosteroids should be considered due to secondary insufficiency of the adrenal glands. Although recommended by some authors, recent data suggest that stress-dosed steroids may not be necessary, even in patients with confirmed pre-operative secondary suppression of the hypo-thalamic-pituitary-adrenal axis. Instead, these patients may be maintained on their usual pre-operative dose and treated with rescue dose steroids only if refractory hypotension occurs in the peri-operative period [11,29].

Immunosuppressive therapy might be related to a higher risk of (post-operative) infectious complications.

The patient's scheduled and regular medication used to maintain mast cell stability should be continued throughout the peri-operative phase [3,9,14].

Anaesthetic procedure

Pre-operative evaluation: see details above.

Premedication: the control of anxiety and stress to avoid trigger stimuli for mast cell degranulation is of importance. As non-pharmacological measure, the case should be scheduled as the first of the day whenever possible. Furthermore, some general precautions like a quiet environment in the operating room during anaesthesia induction and creation of a relaxing and comfortable atmosphere is likely to reduce pre-operative anxiety [14,44]. Adequate sedating premedication (as well as avoidance of certain physical stimuli) can decrease the risk by 10-fold [21]. Therefore, premedication should be performed by weighing the benefits and risks in individual patients. Especially general anaesthesia, major surgery as well as cardiac and gastrointestinal surgery, rank among the high-risk procedures legitimating premedication in SM patients. Sedating premedication may be done, e.g., with midazolam or dexmedetomidine [16,21]. The use of antihistaminergic agents for sedation might be a pragmatic option to combine prophylaxis and sedation.

Many patients with known SM were diagnosed in a SM reference centre (usually haematological, allergological or dermatological centres). This fact results in adequate patient education, written individualised SM emergency recommendations as well as a contact address for quick referral.

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Furthermore, in order to prevent anaphylactic reactions in patients with SM, there are different prophylaxis protocols, using steroids (e.g, methylprednisolone, prednisone, hydrocortisone), dexchlorpheniramine, sodium cromoglycate, leukotriene-receptor antagonists (e.g., montelukast) and/or histamine-1/-2-blockers (e.g., cimetidine, famotidine, roxatidine, hydroxyzine, epinastine, dimetindene, terfenadine, levocetirizine, clemastine, diphenhydramine, chlorpheniramine) [3,4,16,18,21,22,28,42,46]. Aspirin for premedication is under discussion to prevent hypotensive episodes, because this prostaglandin synthase inhibitor may function as both a prostaglandin D2 mediator and a trigger of mast cell degranulation [19,28,36, 39,48]. Nevertheless, pretreatment regimens have been based on accumulated case reports and a real superiority was not demonstrated in placebo-controlled trials for any of them [14,18,19,26]. Besides, precise advice concerning specific medication for premedication as well as its dosage and exact point of application is lacking. Regarding these substances, there are reports of prophylactic administration over several days, hours or at least shortly before scheduled surgery, suggesting some benefit compared to administration only in case of anaphylaxis and occurrence of extensive degranulation [18,21,31]. One retrospective analysis including a large series of adult paediatric patients showed that undergoing the same anaesthetic procedure several times is better tolerated with a reduced number of critical incidences, when prophylactic antimediator therapy and benzodiazepines are administered about one hour before the procedure [31].

The availability of catecholamines, antihistamines, bronchodilators and intravenous fluids should be guaranteed for all patients with SM in the peri-operative period [19,26]. Although the cause of shock in these patients is a non-IgE-mediated immediate hypersensitivity reaction and not a true allergic disorder, it is responsive to epinephrine. Therefore, especially epinephrine should be readily available at any time when taking care of patients with SM [8].

Patient positioning: see above.

IV line: No difficulties due to SM have been reported. One might consider placing a large bore venous access in high risk patients for volume application in case of haemodynamic deterioration. A slow and careful injection of intravenous drugs is recommended due to potential histamine release.

Invasive blood pressure measurement: liberal recommendation to permit rapid response to the potential haemodynamic impairment of mast cell degranulation if the risk is not low [19].

Anaesthesia: Depending on individually known triggers of anaphylactic reactions in patients with SM, total intravenous or balanced anaesthesia using volatile anaesthetics can be safely performed. Drugs previously having caused adverse reactions and/or tested positive on subsequent allergy testing should be avoided [3].

Some anaesthetic drugs can cause histamine release and should be avoided whenever possible, especially if equally effective drugs can be used (e.g., succinylcholine, mivacurium, atracurium, thiopental, lidocaine, procaine, bupivacaine, codeine, pethidine, tramadol and morphine) [18,21,44,46,48]. Nevertheless, some reports show the use of these substances in patients with SM without any problems [9,42].

The use of fentanyl, sufentanil, remifentanil, midazolam, etomidate, propofol, ketamine, pancuronium and rocuronium (even in high dose for rapid sequence induction) is reported as uneventful and recommended for induction. If no rapid onset of relaxation is required, cis-atracurium and vecuronium would be the relaxants of choice whereat the latter one is by the way reported as uneventful for relaxation [2,4,12,18,19,21,27,46].

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Maintenance of anaesthesia is additionally reported without difficulty for volatile anaesthetics (e.g. isoflurane, sevoflurane, enflurane, desflurane, nitrous oxide) as well as some intravenous drugs like propofol and sufentanil [2,18,22,28,42,46].

Muscle relaxant reversal may be done with sugammadex, atropine and neostigmine [18,46]. However, as neostigmine application might result in bronchial hyperreagibility and acute bronchial obstruction and is contraindicated in asthma patients, we discourage its routine use in SM patients.

The named substances may be used with relative safety, nevertheless an absolute guarantee cannot be given. However, considering the current limited literature, there is conflicting information on tolerance/reactions to various drugs. Essentially, general recommendations regarding these substances cannot be given. Besides, following advice from non-evidence-based lists of drugs to be avoided may lead to problems in finding suitable post-operative analgesics, as avoidance of several drug groups such as local anaesthetics, opioids, and NSAIDs is often suggested [3].

To support intra-operative and post-operative pain management in patients with SM, regional anaesthesia may help to avoid episodes of severe pain as possible triggers for mast cell degranulation [18].

(Mechanical) ventilation: There are no specific recommendations. A lung-protective strategy with adequate low tidal volumes should be applied to avoid baro-/volutrauma.

Malignant hyperthermia: no specific risk known.

Particular or additional monitoring

To detect extreme changes in temperature as possible triggers for mast cell degranulation, the body temperature should be monitored continuously whenever possible. The use of warming mats as well as warmed intravenous fluids is recommended to aspire normothermia [4,14,18].

In the event of an anaphylactic incident, particularly if SM is suspected as the cause, the serum tryptase level can be monitored to aid diagnosis [26]. It has a half-life time of two-and-a-half hours, peaks within one hour in anaphylaxis-like incidents and will not typically fall to normal levels for four to twenty-four hours after occurrence [5,26]. Histamine levels (in blood or urine) alone are not helpful to diagnose an incident related to SM, because its serum half-life (approximately 30 minutes) is usually shorter than the time needed to suspect this diagnosis [26].

Possible complications

Hypersensitivity reactions up to an anaphylactic shock [22].

Cardiovascular collapse of different degrees, bronchospasm, and respiratory impairment up to death in patients with SM undergoing general anaesthesia are documented [48].

Kounis syndrome (acute coronary syndrome/myocardial ischaemia with mast cell activation in a setting of allergic or hypersensitivity reactions) [17].

Infections in case of fulminant immunosuppression.

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Post-operative care

The peri-operative course of patients with SM remained uncomplicated in most of the reported cases [14]. Nevertheless, their peri-operative management involves a multi-disciplinary approach [13].

At least, post-operative care should be based upon the patient's pre-existing conditions as well as the surgical or interventional procedure. Nevertheless, even in cardiorespiratory healthy patients, one should reckon with deterioration due to flush or (late-onset) anaphylactic reactions any time [5,22]. Close monitoring is recommended as well as avoidance of drugs carrying risk of mast cell degranulation as well as (co-)stimulating factors like changes in room temperature or skin exposure to pressure/friction .

Epinephrine and further emergency drugs should be available in the post-operative setting [21].

There are reports of mild post-operative episodes including, e.g., abdominal cramps, pruritus or flushing [42]. However, especially in cases of anaphylactic reactions during anaesthesia and surgery, the patient should be monitored during an appropriately extended period of time in the PACU or IMC (presupposed a haemodynamic and respiratory stability) before transfer to the normal ward (or discharge at home) will be acceptable. Otherwise, post-operative care and monitoring should be performed in the ICU setting [22].

An excellent post-operative pain management is essential for patients with SM, because severe episodes of pain may trigger massive mast cell degranulation [14,18]. NSAID can be carefully considered in patients who have been treated with these drugs in the past without incidents [3,27].

There are reports of prophylactic steroid (methylprednisolone, prednisolone, prednisone, hydrocortisone) as well as leukotriene-antagonist (e.g., montelukast) and antihistaminic drug (ranitidine, cetirizine) application for the first few post-operative days [16,18]. Subsequent gradual tapering of drug doses is recommended [12]. Pre-operative existing antihistaminic long-term medication should be continued as usual.

In cardiac surgery, the use of a cardiopulmonary bypass (CPB) is potentially related to a higher level of mast cell degranulation. Additionally, protamine used to antagonise heparin for the CPB has a high potential for acute degranulation. We thus recommend a liberal SM prophylaxis including corticosteroids and antihistaminergic drugs as well as a stepwise and slow application of protamine after CPB [37,43].

Apart from the pre-operative baseline level, serum tryptase may also be quantified post-operative to compare both values and evaluate the possibility of hypersensitivity reactions [18,46].

Disease-related acute problems and effect on anaesthesia and recovery

Emergency-like situations (from hypersensitivity/anaphylactic reactions up to shock situations). The treatment of these incidents in SM is aimed at stabilising the mast cell membrane and preventing release of or antagonising the effects of released mediators [16].

Differential diagnostics (digestive (e.g., gluten enteropathy, coeliac disease, irritable bowel), endocrinological (e.g., pheochromocytoma, carcinoid syndrome), autoimmune (i.e., vasculitis) or neurological conditions (i.e., depression, fibromyalgia), mast cell activation

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syndrome (MCAS)) [39]. In case of cardiovascular impairment, myocardial infarction, tension pneumothorax or pulmonary embolism as well as other causes of cardiac arrest should be ruled out, e.g., by laboratory, electrocardiographic, and echocardiographic investigations [41].

Ambulatory anaesthesia

Specific recommendations for or against ambulatory anaesthesia cannot be given as there is no published literature on this topic. There is also no evidence that patients with SM are not candidates for ambulatory surgery or anaesthesia. However, one should consider the possibility of delayed reactions and patients need to be enlightened about this [14,44]. Therefore, these patients may rather not be considered as appropriate candidates for ambulatory care [27].

Obstetrical anaesthesia

SM does not seem to significantly influence fertility. Thus obstetrical anaesthetists might face women with SM for labour analgesia. A well-structured anaesthetic plan for delivery should be established, discussed with the parturient and communicated to all team members involved at the earliest opportunity to avoid complications [10,44].

Due to e.g. physical and emotional stress and possible discontinuation of antimediator drugs during pregnancy, anaesthetists should be aware of pregnancy and delivery as potential stressors for mast cell degranulation and activation of the disease. Therefore, pregnancy and delivery may be associated with potential complications of SM as well as preterm labour [10,25,30]. Nevertheless, regarding the absolute risk for anaphylaxis in these patients as well as prophylaxis and optimal treatment, randomised studies are lacking.

Apart from reported vaginal delivery, the necessity of Caesarean delivery due to SM is possible. Neuraxial (spinal as well as epidural) and/or general anaesthesia might be performed in this patient population [10,44]. A comfortable setting and an early epidural administration of analgesia may even minimise stress and anxiety and provide an adequate analgesic level to decrease the possibility of mast cell degranulation [14,25]. Many authors prefer ropivacaine as the local anaesthetic of choice. However, there are also reports about the safe use of bupivacaine [42,44]. Severe complications due to anaesthesia are not reported except for mild symptoms like pruritus or erythema after epidural anaesthesia for labour [10,30]. Exacerbation of SM with hypotension and difficulty breathing requiring intravenous epinephrine is reported a few minutes after delivery in one patient [49]. However, the lack of reports in obstetrical anaesthesia should result in proper shared decision-making regarding the selection of anaesthesia techniques for specific women.

Pregnancy seems to have only slight effects on the intensity and frequency of symptoms related to SM. Worsening of disease-related symptoms (e.g., pruritus, urticaria, skin lesions, fatigue) occurs in about 20–30 % of patients with mastocytosis [10,39]. One study documented idiopathic anaphylaxis during pregnancy in 9 % of the study population [30]. Increased oestrogen levels and hormonal changes are thought to be causative for potential disease progress during pregnancy [10,30]. Although conclusive data are still missing, most case reports about anaphylaxis in pregnant women with SM in the vast majority comprise the indolent form. Therefore, advanced SM patients seem to be less prone to get anaphylaxis as compared to ISM patients.

A well-equipped setting as well as several emergency medications, such as glucocorticoids, antihistamines and especially epinephrine, should be available during the critical phases of labour and in the early postpartum period [10,25,39]. The prophylactic administration of second-generation antihistamines to pregnant women with mastocytosis still raises many controversies [10].

Anaesthesia and surgical procedures in the SARS-CoV-2 pandemic

Due to a lack of data, the possible role of mast cells in coronavirus infections remains uncertain and it is unknown whether these cells play a defensive or accelerating role in COVID-19 [47]. Nevertheless, most patients with SM appear to have normal cellular and humoral immune systems and there is no evidence that patients with SM have a higher risk to acquire a SARS-CoV-2 infection or to develop severe COVID-19 [47]. With respect to a continuous treatment with glucocorticoids, other immunosuppressive drugs, chemotherapy, or comorbidities (e.g., arterial hypertension, pulmonary disease, or diabetes mellitus), this must be considered for each individual SM patient [47]. Because many of these patients avoid public meetings and crowded places, for example, their risk for an infection as well as the distribution of SARS-CoV-2 may be lower regarding the general population [47].

Patients on anti-mediator-based treatment should continue therapy, with recognition that potential drug-drug interactions might occur between antihistamines such as antiviral and other drugs used in the coronavirus context. Beside general hygiene policies, another preventive measure may be the avoidance or dose-reduction of a treatment with glucocorticoids or immunosuppressive agents, if arguable. Furthermore, there is no evidence that antiviral drugs (e.g., remdesivir) induce or aggravate mast cell activation in SM patients [47].

Early testing of SM patients is recommended. Patients showing signs of progression of SARS-CoV-2 infection as well as patients requiring antiviral therapies should be hospitalised.

Treatment of COVID-19 should be based on the local guidelines considering that these patients have a low but measurable risk to show symptoms related to mast cell mediator release or even anaphylaxis [47]. Once available, vaccination for SARS-CoV-2 will be recommended for all SM patients [47].

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