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Systematic Review

Protective Treatments against Endothelial Glycocalyx Degradation in Surgery: A Systematic Review and Meta-Analysis

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Abstract: The aim was to explore the body of literature focusing on protective treatments against endothelial glycocalyx degradation in surgery. A comprehensive systematic review of relevant articles was conducted across databases. Inclusion criteria: (1) treatments for the protection of the endothelial glycocalyx in surgery; (2) syndecan-1 used as a biomarker for endothelial glycocalyx degradation. Outcomes analysed: (1) mean difference of syndecan-1 (2) correlation between glycocalyx degradation and inflammation; (3) correlation between glycocalyx degradation and extravasation. A meta-analysis was used to present mean differences and 95% confidence intervals. Seven articles with eight randomised controlled trials were included. The greatest change from baseline values in syndecan-1 concentrations was generally from the first timepoint measured post-operatively. Interventions looked to either dampen the inflammatory response or fluid therapy. Methylprednisolone had the highest mean difference in plasma syndecan-1 concentrations. Ulinastatin showed correlations between alleviation of degradation and preserving vascular permeability. In this systematic review of 385 patients, those treated were more likely than those treated with placebo to exhibit less shedding of the endothelial glycocalyx. Methylprednisolone has been shown to specifically target the transient increase of glycocalyx degradation immediately post-operation and has displayed anti-inflammatory effects. We have proposed suggestions for improved uniformity and enhanced confidence for future randomised controlled trials.

Keywords: endothelial glycocalyx; inflammatory response; fluid loading; surgery; post-operative; albumin extravasation

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1. Introduction

The vascular endothelium plays several important roles including haemostatic balance, endothelial integrity, and blood flow regulation [1]. It comprises a single layer of endothelial cells, lining every blood vessel in the body and is understood to be 4000–7000 m^2 [2]. These cells play a vital role as a semipermeable membrane to allow the exchange of nutrients and the removal of waste to and from the blood. A key structure involved in these actions is the endothelial glycocalyx (EG), which coats cells' extracellular matrix. EG thickness ranges from 0.2 µm in capillaries to 4.5 µm in the carotid artery [3]. The glycocalyx enables changes by a process known as mechanotransduction.

Mechanotransduction is the mechanism by which external mechanical stimuli are converted into cellular responses through signalling pathways [4]. The apical surface of the glycocalyx consists of glycosaminoglycans (GAGs); those commonly associated with the vasculature are heparan sulphate (HS), chondroitin sulphate (CS) and hyaluronic acid (HA) [5]. Additionally present are syndecans, which provide sites on the apical surface to highly regulate proteolytic cleavage. The best conceptual theory for glycocalyx to detect

changes in blood flow was described by Squire [6] as the "wind in the trees". The wind (fluid flow) is sensed by the branches (GAGs) of which the drag force is transmitted through the trees/forest (glycocalyx) and stimulates a response. Twenty-four-hour exposure of fluid shear-stress (FSS) in an in vitro model of EG has been shown to enhance synthesis and distribution of the prevalent components (HS, CS, and HA) of the glycocalyx with nearly normal uniform spatial distribution, similar to baseline levels compared to only 30 min of exposure [7].

Surgery is associated with EG degradation [8]. A suggested mechanism for this is that the thickness of the glycocalyx, and thus the surface layer, is reduced by ischaemia/reperfusion [9]. This increases capillary permeability and, thereby, contributes to tissue oedema (Figure 1) [10]. EG degradation is known to disrupt the equilibrium between pro-inflammatory cytokines and adhesion molecules, and vasodilators and vasoconstrictors, leading to endothelial dysfunction [11]. Glycocalyx components are released, such as syndecan-1 and heparan sulphate, during surgery. However, the steps in which diseases, trauma, and surgery thin the EG are not well understood. Johansson et al. [12] undertook a prospective 75-patient double-blind cohort study and found trauma patients to have raised plasma syndecan-1 levels associated with 16 other markers for inflammation, and tissue and endothelial cell damage. Patients with significant EG degradation were shown to have a three-fold increase in mortality compared to those with lower syndecan-1 levels. A mechanism to explain the strong association between EG degradation and patients with trauma is through the extensive activation of the inflammatory and coagulation pathways. Protection against EG degradation could help treat against known diseases to shed major EG constituents, such as diabetes and hyperglycaemia, atherosclerosis and chronic kidney disease [13].

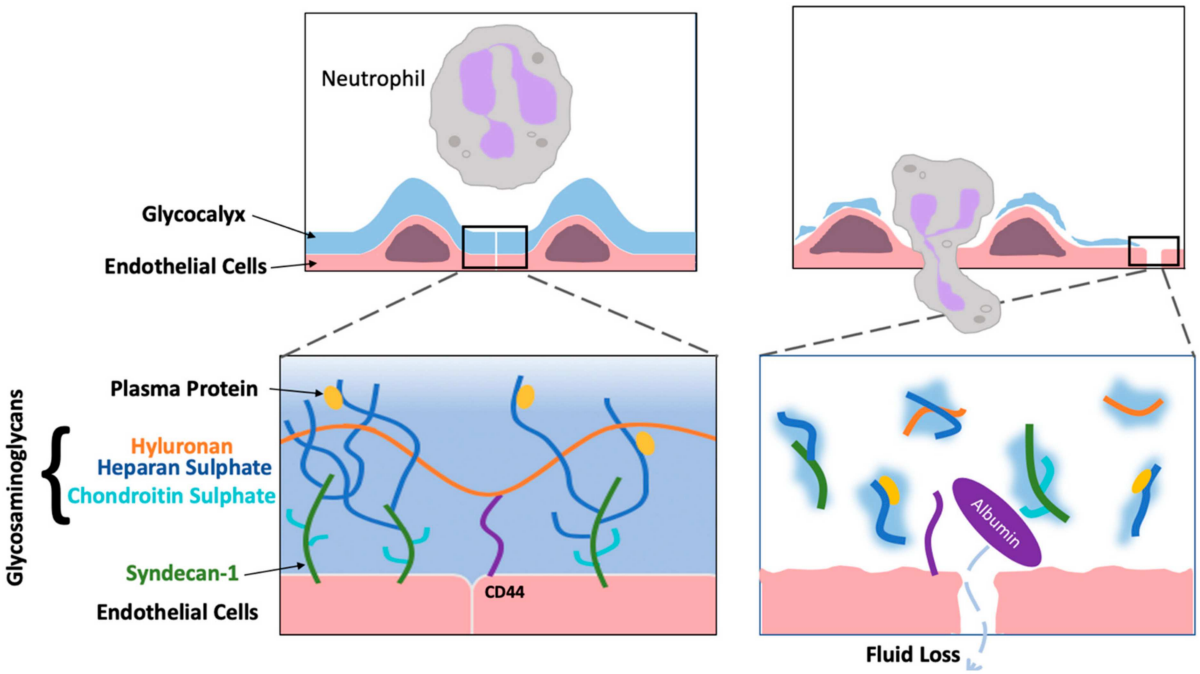

Figure 1. EG structure during health (**left**) and degradation (**right**). Disease causes thinning of the glycocalyx. Glycocalyx constituents are released into the plasma. An inflammatory response is produced with the recruitment of leucocytes and the loss of fluid.

Recent studies have looked into pharmacological interventions to prevent EG degradation during surgery. With the limited studies, interventions have looked into two therapeutic routes: (1) dampening the inflammatory response and (2) fluid-therapy. (1) The EG plays an important role in the post-injury inflammatory response [14]. An increase in C-reactive protein (CRP) has been associated with a decreased thickness of the EG and

impaired vasoreactivity [15]. (2) Infused fluid therapy has been associated with impaired microcirculation, resulting in tissue oedema. Moreover, fluid infusion could cause EG degradation and further fluid loss into the lymphatic system through albumin and other plasma proteins moving across the vascular wall [16].

This systematic review and meta-analysis looks to examine the body of literature into protective treatments for EG degradation in surgery from most of the published clinical trials. The aim is to identify trends in treatments which may address the mechanism for which surgery causes EG degradation.

2. Materials and Methods

2.1. Search Strategy

A comprehensive review of the literature was conducted in May 2020, using databases, such as Cochrane Library of Systematic Reviews, Cochrane Central Register of Clinical Trials (CENTRAL), MEDLINE, PubMed, and Clinical Trials.org. Article selection was limited to publications in the English Language between 1 January 1950 and 20 May 2020. Search terms used were a combination of the following: "endothelial", "glycocalyx", and "degradation". Reference lists of the selected articles and other related studies were assessed for eligibility. Cross-referencing from identified articles and conference abstracts were also performed. Clinical trials which are currently in progress with no data available were not included.

2.2. Inclusion Criteria

One researcher (H.K.) performed the review process for inclusion in the systematic review. Specific inclusion criteria mandated systematic reviews and clinical trials that were from retrospective or prospective investigations which met the following criteria; (1) papers published in the English Language; (2) clinical investigations into protective treatments for EG; (3) syndecan-1 used as a biomarker for EG degradation (specific marker for significant degradation as opposed to HS for minor disturbances); (4) clinical investigations in which patients were followed from pre-operative/induction of anaesthesia to the end of surgical treatment [17].

2.3. Exclusion Criteria

From the search strategy, 987 studies were selected. The first screen excluded articles if they had not conducted investigations on surgical patients. A further screen excluded articles that investigated combined treatments and those in which more than one substance was administered during surgery.

After exclusion, 112 articles formed the inclusion of the initial review. Following this, an independent abstract review was conducted by the same author for the title review. Three were removed as they investigated the role of the EG within surgery without the use of an intervention. One assessed the microperfusion abilities of endothelial cells following surgery. Twenty-nine articles investigated the effects of surgery (cardiothoracic, abdominal, hysterectomy, etc.) on the EG and whether surgery is a stimulatory factor for EG degradation. Twelve articles looked into protective biological factors and signalling pathways of the body that are used to protect against EG degradation in surgery. Twenty-one articles were trials conducted on animals/in-vitro models. Twenty-nine articles investigated the effects of different surgical procedures had on the structural integrity of the EG. Six articles were related to the effects that degradation of the EG had on other systems.

The final screen of 11 articles in their entirety was completed by the same researcher (Khan, H) to ensure adequate data content for inclusion in the systematic review. One had been centred on post-operative interventions which focuses more into regeneration/recovery of the EG [18]. Three articles were excluded as they were clinical trials still undergoing with no preliminary results [19–21].

After the full text review, the final search included 7 articles that met the inclusion criteria and thus were used for analysis and data were extracted (Brettner et al. [22];

Kim et al. [23]; Lindberg-Larsen et al. [24]; Mennander et al. [25]; Nemme et al. [26]; Pesonen et al. [27]; Wang et al. [28]). The search strategy has been depicted in Figure 2.

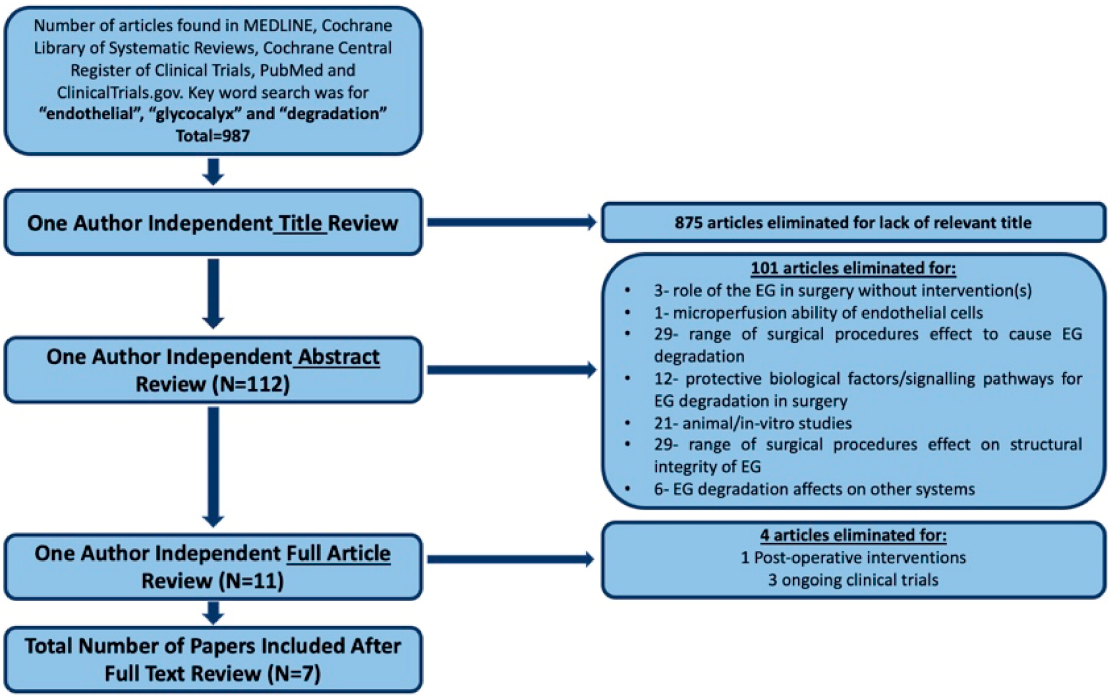

Figure 2. PRISMA flow chart of search strategy to identify pivotal publications of protective treatments against EG degradation in surgery for meta-analysis.

2.4. Data Extraction

Data were extracted and then reviewed, and all reported results were summarised to include comparable and clinically relevant outcomes. The following data were extracted from each clinical trial and used for descriptive comparison; author, year, study design, sample size, surgery, type of treatment, time points for administration of treatment (and/or placebo), biomarkers used to measure endothelial cell glycocalyx degradation, time points used for biomarker measurements (Table 1), and details regarding degree of endothelial cell glycocalyx degradation and post-surgical complications (Table 2).

2.5. Statistical Analyses

Using GraphPad Prism version 8, a line graph was produced to assess the change in plasma syndecan-1 concentrations in the control groups of the included articles. This enabled identification of the timepoints at which to expect interventions to target. This analysis formed the basis of a forest plot. Some articles provided checkpoints in surgery for when blood samples were taken rather than averaged time-points of each sample. The provided averaged times for each stage in surgery were converted to averaged timepoints when blood samples were taken. Meta-analysis was conducted using RevMan 5.4 from Cochrane Review to derive pooled effect estimates as a mean difference associated with 95% confidence intervals. The effect on the analysis of within and between study heterogeneity was quantified by calculating I^2. Overall, 4 studies with 5 randomised controlled trials were included for the forest plot.

Table 1. Publications included for review of protective treatments for EG degradation in surgery.

Reference	Sample Size	Study	Controlled	Comparative	Patients Age	Syndecan-1 Marker	Surgery	Anaesthesia	Treatment (Drug Class)
Pesonen et al. (2016) [Neonates] Pesonen et al. (2016) [VSD]	40 45	Prospective	No	Yes	7 (1–27) 0.37 (0.15–1.36)	Yes Yes	CPB	Sufentanil, Pancuronium, S-ketamine Maintained-> Sevoflurane	Methylprednisolone (Corticosteroid)
Brettner et al. (2019)	30	Prospective	No	No	65 (57.3–74)	Yes	CPB	Midazolam, Sufentanil, Pancuronium Maintained-> Sufentanil	Hydrocortisone (Corticosteroid)
Wang et al. (2017)	50	Prospective	No	Yes	58.56	Yes	VATS Lobectomy	Midazolam, Propofol, Sufentanil-> Propofol, Remifentanil, Rocuronium	Ulinastatin (UTI, anti-inflammatory agent)
Lindberg-Larsen et al. (2017)	63	Prospective	No	Yes	63.27	Yes	Unilateral Total Knee Arthroplasty	Standard procedure	Methylprednisolone (Corticosteroid)
Nemme et al. (2019)	24	Prospective	No	No	47(5) 46(4)	Yes	Hysterectomy	Midazolam, Fentanyl, Propofol	Ringers Lactate (Fluid Therapy)
Mennander et al. (2012)	13	Prospective	No	Yes	Not stated	Yes	CPB	Propofol, Sufentanil, cis-atracurium Maintained-> Sevoflurane	Diazoxide (Thiazide)
Kim et al. (2017)	120	Prospective	No	No	67.8 (9.9) 65.3 (10.5)	Yes	CPB	Midazolam, Sufentanil, Vecuronium Miantained0> Remifentanil, Propofol	Hydroxyl Starch (Crystalloid Starch Fluid Therapy)

Table 2. Outcome on EG degradation.

Reference	Timepoints	Syndecan-1 Levels	Timepoints of Statistical Significance	Heparan Sulphate	Inflammatory Markers	HGB and Albumin	Hyluronan
Pesonen et al. (2016) [Neonates] Pesonen et al. (2016) [VSD]	T1: induction of anaesthesia T2: 30-min on CPB T3: weaning of CPB T4: 6-h post-operative	Significant lowering in intervention group to none in control group, when comparing to baseline values None	T1->T2 N/A	N/A N/A	N/A N/A	N/A N/A	N/A N/A
Brettner et al. (2019)	T0: preoperative T1: induction of anaesthesia T2: 30 min after onset of CPB T3: weaning of CPB T4: 1-h post-operative T5: 4-h post-operative	None	N/A	T2–3	Higher CRP post-operatively on Days 1,2,3 in control to intervention group, when comparing to baseline values Higher IL-6 on Day 2 post-op in control to intervention group, when comparing to baseline values	N/A	N/A
Wang et al. (2017)	T0: preoperative T1: end of surgery	Control group showed a significant increase with none in intervention group, when comparing to baseline values	T0->T1	None	N/A	Significant lowering of albumin in control to intervention group, when comparing to baseline values	N/A
Lindberg-Larsen et al. (2017)	T0: pre-operative T1: 2-h post-operative T2: 6-h post-operative T3: 24-h post-operative	Control group showed a significant increase with none in intervention group	T0->T3	N/A	No effect on sE, prevent significant drop in thrombomodulin, Reduced increase in VEGF in intervention to control, CRP increased less so in intervention group, when comparing to baseline values	N/A	N/A

Table 2. *Cont.*

Reference	Timepoints	Syndecan-1 Levels	Timepoints of Statistical Significance	Heparan Sulphate	Inflammatory Markers	HGB and Albumin	Hyluronan
Nemme et al. (2019)	T0: pre-operative T1: 30-min intra-operative T2: 60-min intra-operative T3: 90-min intra-operative T4: 2-h post-operative	Significant increase from baseline values in both groups	T3->T4	T3->T4	Some patients showed raised CRP post-operatively However, only results for some were significant	Albumin showed similar trends to HB but lower No significant differences at time points The greatest difference of values was at 20 min but lowered significantly at 90 min	N/A
Mennander et al. (2012)	T1: induction of anaesthesia T2: after aortic clamp removal T3: 60-min intra-operative T4: closure of skin wound	Significant drop found in intervention group of which control group did not show, when comparing to baseline values	T2->T3 T3->T4	N/A	N/A	N/A	Similar changes to syndecan-1 levels
Kim et al. (2017)	T1: induction of anaesthesia T2: 60-min after coronary artery anastomosis T3: upon infusion of HES/crystalloid T4: skin closure T5: 12-h after ICU admission	None	N/A	N/A	N/A	N/A	N/A

3. Results

3.1. Description of Included Studies

The articles included were published in 2012–2019. Sample sizes varied from 16 patients [25] to 120 patients [23]. From the remaining 6 articles, patients' median age ranged from 7 months [27] to 67.8 years-old [21]. One article did not provide any information for patient average age [25]. Four articles did not include a range for the patients' ages [23,24,27,28] but a standard deviation. From the remaining 2 articles that included patient's age range, the range was from 1 month to 72 years-old.

Two articles described two treatments using different sample groups with no control group [23,25]. The remaining 5 articles investigated their treatment using two patient groups (control vs. intervention). One article conducted two separate randomised, prospective clinical trials by testing the intervention on two different patient cohorts based on age and surgical procedure [27]. All articles had delivered their drug following the administration of anaesthesia. Of the articles to investigate protective interventions for EG degradation, 4 looked into CPB [22–24,26], 1 into abdominal hysterectomy [26], 1 in knee replacement surgery [24] and 1 in pulmonary lobe resection [28].

3.2. Outcomes and Results

When analysing the included articles of our systematic review, the focus was on (1) the comparison between control and intervention groups to reduce levels of EG degradation in surgery; (2) correlations between glycocalyx degradation and an inflammatory response; and (3) correlation between glycocalyx degradation and extravasation. For each study, we assessed biomarkers for glycocalyx degradation (syndecan-1, and those that measured HS), as well as those that measured inflammatory markers and capillary leakage.

Four studies investigated the protective treatments against degradation of the EG in CPB [22,23,25,27]. Only 2 studies [25,27] showed a significant lowering of plasma syndecan-1, which in both cases occurred during surgery. The Mennander [25] study, which investigated the effects of diazoxide, found similar changes in hyaluronan ($p < 0.04$ and $p < 0.04$ respectively). The Brettner study [22] investigated the effects of hydrocortisone. There were no significant differences in plasma syndecan-1 levels between intervention and control groups. However, they did establish significant lowering of HS levels intra-operatively. The Kim study [23] differed from the other clinical trials by comparing two interventions; hydroxyl starch (HES) vs. crystalloid. It has also differed from the other studies as patients had undergone off-pump CPB, which is of clinical significance as studies have shown differences in plasma syndecan-1 and plasma heparan sulphate concentrations between surgeries [29]. Following infusion of 20 mL/kg of the study fluids, median syndecan-1 levels were higher in the HES group than the crystalloid group [(79.7 (46.6–176.6) vs. 62.7 (30.1–103)]. However, overall peri-operative changes in syndecan-1 were not significantly different between the groups.

Of the 4 selected articles, the Brettner study [22] was the only to investigate the inflammatory response in addition to glycocalyx degradation. There was significant lowering of CRP levels on days 1, 2 and 3 post-operatively in the hydrocortisone group (p is 0.014, 0.012 and 0.022 respectively). Interleukin-6 (IL-6) was significantly lower in the intervention group to the control group ($p < 0.05$).

One study [27] used urinary trypsin inhibitor (UTI) to treat EG degradation in video-assisted thoracoscopy (VATS) lobectomy. There were no significant differences in baseline values of syndecan-1, HS, HGB and serum albumin levels in the control and UTI group. However, syndecan-1 levels were elevated at T1 in the control group (3.77 ± 3.15 versus 4.28 ± 3.30, $p = 0.022$), whereas the UTI group showed no significant increase at T1 (3.98 ± 3.04 versus 4.24 ± 3.12, $p = 0.160$). There were no obvious changes in HS levels between groups.

One study looked into the effects of pre-operative methylprednisolone treatment in total knee arthroplasty [24]. Syndecan-1 concentrations remained stable in the control group with a statistically significant drop from baseline to 24-h post-operative (14.1 ± 1.4

versus 12.4 ± 12.4, $p = 0.001$). Vascular endothelial growth factor (VEGF) increased in both groups with only a transient increase in the methylprednisolone group (T0->T6: 42.4 (2.5) to 54.8 (4.1), $p = 0.008$ versus 37.7 (2.5) to 47.7 (4.9), $p = 0.019$). Soluble thrombomodulin (sTE) increased in both groups but only transiently in the methylprednisolone group (T0->T6: 5.0 (0.2) to 5.4 (0.3), $p = 0.008$ versus 5.0 (0.2) to 5.2 (0.4), $p = 0.022$). CRP increased in both groups but less so in the methylprednisolone group (T0->T24: 4.5 (1.1) to 36.6 (3.6) versus 6.9 (2.2) to 74.4 (5.0)). Overall, effects of methylprednisolone were more pronounced at higher base values in sTM, sE-Selectin and VEGF (p =0.012, $p = 0.009$ and $p < 0.001$, respectively) but this was not the case for syndecan-1.

One study looked into the effects of ringer's lactate (a form of fluid therapy) to prevent EG degradation in abdominal hysterectomy [26]. This article differs from other included studies, as the two groups were based on different anaesthetic medications (propofol or sevoflurane), with no control group. Plasma syndecan-1 and HS levels showed minimal variations during surgery but significantly increased 2-h post-operatively ($p < 0.05$ and $p < 0.001$, respectively, between 90 min and 2 h, compared using Wilcoxon's matched-pair test). Plasma concentrations for brain natriuretic peptide (BNP) showed small changes but no significant differences between groups.

There was a common significant increase in plasma syndecan-1 concentrations between baseline values and the first time-point post-operation. Data from the articles plotted (Figure 3) showed similar baseline values compared with their corresponding intervention group. Hence, we used the first timepoint post-operation from each article as the basis for the forest plot (Figure 4). Patients receiving diazoxide in CPB, methylprednisolone in CPB for neonates, methylprednisolone in VSD trial, methylprednisolone in total-knee arthroplasty, UTI in VATS lobectomy, had pooled mean differences of −1.4 (95% CI: −3.67, 0.87), −83.1 (95% CI: −150.4, −15.8), −59.0 (95% CI: −96.97, −21.03), −10 (95% CI: −20.79, 0.79) and −0.1 (95% CI: −9.0, −9.80), respectively.

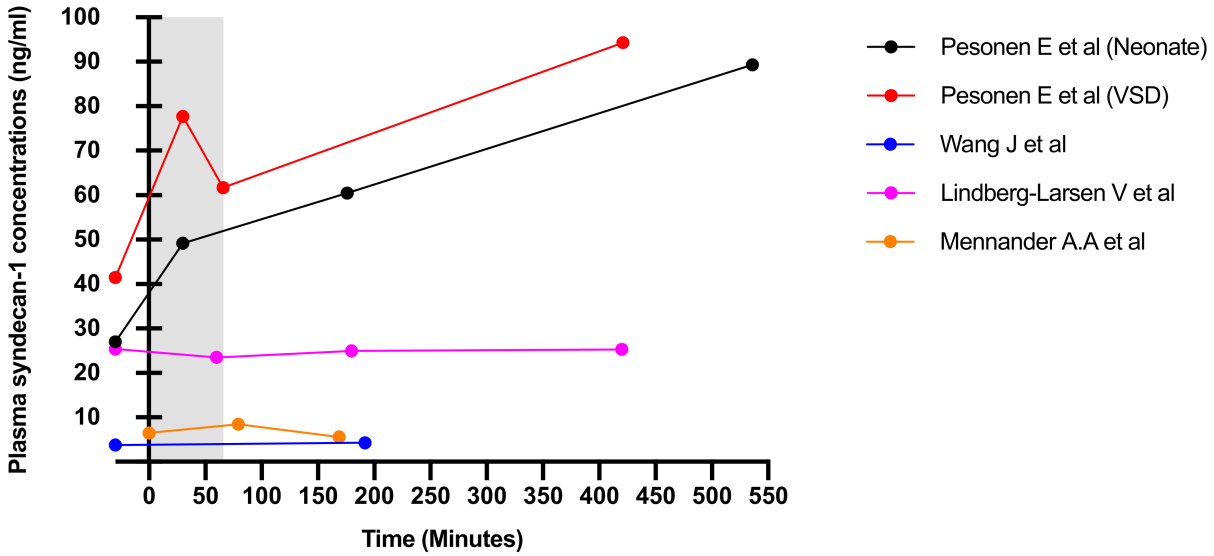

Figure 3. Changes in plasma syndecan-1 concentration in the control groups of the included articles. Values lower than x = 0 represent blood samples taken pre-operative. Values within the grey region are samples recorded intra-operatively.

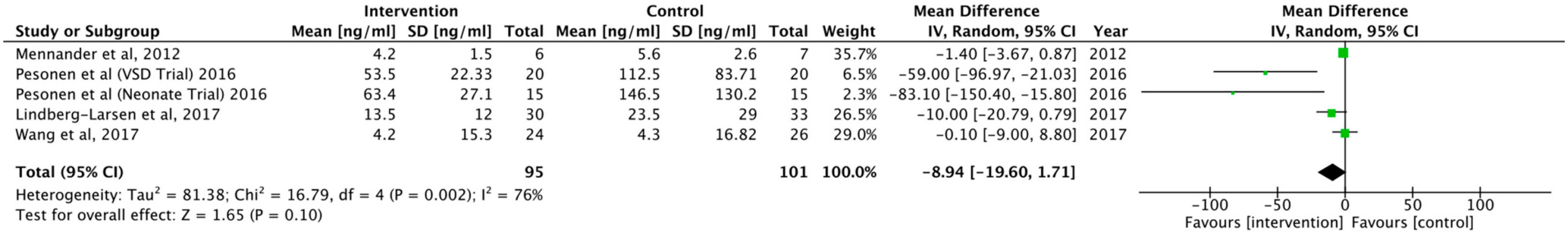

Figure 4. Forest plot of the mean difference of plasma syndecan-1 concentration changes for treatments to protect against EG degradation in surgery.

4. Discussion

To the authors' knowledge, there has been no systematic review to investigate treatments to protect against EG degradation in surgery. In our study, the greatest change in plasma syndecan-1 concentrations from baseline values, was generally found at the first timepoint measured post-operatively. Syndecan-1 is a marker for greater trauma of EG shedding, so more time may be required for this extent of damage to occur and to be detected. The transient increase can be explained by the proteolytic degradation of the glycocalyx with subsequent rapid clearance, especially via the kidneys [30]. A slow systemic degradation could be explained by a general activation of leucocytes and platelets with an associated release of enzymes that shed the glycocalyx [31]

Pooled data from 196 patients in 5 randomised controlled trials for protective treatments against EG degradation in surgery indicated that patients treated with experimental drugs were more likely to respond than those treated with placebo, with a pooled mean difference of −8.94 (95% CI: −19.60, 1.61). Randomised controlled trials using methylprednisolone were shown to have the greatest effect to inhibit elevation of syndecan-1 levels. This may be important as it provides evidence for the development of personalised interventions, targeting patients in selected groups with altered risk profiles, for example, using bolus I.V. methylprednisolone in patients with high baseline values of endothelial activation and damage. Lindberg-Larsen study [24] found that the effect of methylprednisolone on syndecan-1, sTM and VEGF concentrations was dependant on the time of sampling, with these outcomes increasing with time. Pesonen study [27] showed similar changes in which methylprednisolone failed to inhibit the increase of syndecan-1 shedding at the early time-points, yet showed significant lowering of syndecan-1 levels to its corresponding control group for later time-points. A combination of the previous work on interleukins by Keski-Nisula [32] and these present syndecan-1 results suggest that methylprednisolone probably mediates the conservation of glycocalyx by an anti-inflammatory action. This is operative at the time-points when interleukin production is regulated via de novo protein synthesis due to glucocorticoid receptor activation. Of the three randomised clinical trials, with only one of them to have their upper-confidence interval to go beyond the line of no effect by 0.79 ng/mL, future work on methylprednisolone could be promising to protect the EG in surgery.

Brettner [22] showed hydrocortisone to reduce minor disturbances and not significant degradation of the EG. This shows that mechanistic pathways involved with shedding of heparan sulphate side-chains evoked by the combined stimuli of surgery were more susceptible to inhibition by hydrocortisone than the one leading to cleavage of the transmembrane core protein, syndecan-1. Whilst inflammatory markers (IL-6 and CRP) had shown significantly higher levels in the control group to the hydrocortisone group post-operatively, it had no relevant influence on inflammatory clinical parameters. As highlighted previously, the Lindberg-Larsen study [24] showed the effect of methylprednisolone on syndecan-1, sTM and VEGF concentrations was dependant on the time of sampling, with these outcomes increasing with time. However, this study showed no correlation with changes in CRP and any of the EG degradation markers. Analysis of the Nemme study [26] was challenging with no control group, however, there were no marked changes in BNP, syndecan-1, heparan sulphate and CRP between the two groups. There was no correlation between inflammatory markers (BNP and CRP) and glycocalyx shedding products.

The following results from the three articles differed from their previous research. Experimental studies had shown hydrocortisone to provide EG protective properties, most probably due to the stabilisation of mast cells, and, therefore, the amelioration of histamine, cytokines, lysases and protease production [9,33,34]. Stress doses of hydrocortisone administered before cardiac surgery in high risk patients attenuated systemic inflammation and improved early outcomes [35]. Glucocorticoids, such as methylprednisolone, have been shown in animal studies to reduce oedema formation and shedding of the glycocalyx by reducing the systemic inflammatory response in surgery [36]. Nemme [26] was unable to replicate the typical acute increase in BNPs seen previously experimentally [37,38] and

post-operatively [39]. The included articles did not investigate the association between the degradation of the EG and cytokine production. Further surgical studies should look to understand the association and mechanism between EG shedding and cytokines' influence on endothelial permeability.

A common problem found in each randomised controlled trial was minimal shedding. The two reasons in which minimal shedding could have occurred are (1) the small patient sample and (2) the low operative stress in each clinical trial. Johansson study [12] showed that patients undergoing surgery from significant trauma had elevated syndecan-1 concentrations associated with raised inflammatory markers. This could highlight that significant EG degradation is needed to stimulate an inflammatory response, and hence, allow the action of anti-inflammatory medication to protect and treat against the symptoms.

Wang et al. [28] found a significantly greater decrease in plasma albumin compared with HGB at POD1, suggesting that serum albumin was not only lost as a result of blood loss but also by extravasation and attributed this to increased vascular permeability. Furthermore, serum albumin levels were significantly lower at POD1 in the control group compared to the UTI group, yet HGB levels were similar in both groups. This suggests that serum albumin leakage was reduced as a result of a decrease in microvascular permeability in the UTI group. With the UTI group showing no significant increase in syndecan-1, not only does this provide evidence of association between alleviation of degradation and preserving vascular permeability, it also suggests the development of personalised interventions against oedema formation as a result of surgery. With these findings, it may suggest a mechanism whereby UTI acts to protects the vascular endothelial barrier function during surgery, and therefore reduce tissue oedema. The Nemme study [26], also used the latter approach to investigate fluid maintenance in surgery to protect against EG degradation. A comparison between variables could only be made from the first hour post-infusion, which suggested intravascular albumin leakage out of the bloodstream at a normal rate. However, the data did not support previous work that suggested significant capillary leakage of albumin in response to hypervolemia [40].

Whilst this analysis provides useful information for clinicians for future work, the following limitations should be noted. As with all meta-analyses, the precision of pooled effect estimates is dependent on the sample size. Therefore, of all the included articles which had small sample sizes, greater patient cohorts are needed to be truly representative of the clinical outcomes experienced in the population. We have seen the contradictory evidence of EG degradation in surgery, yet it is well-understood that greater operative-stress does have an impact on endothelial integrity. Where there was a lack of ability to disrupt EG structure, this produced varying degrees of inflammatory responses and albumin leakage. Correlation between EG degradation and inflammatory markers as well as pronounced extravasation were difficult to analyse. Included articles did not investigate the source of EG degradation products produced during surgical operations. Overall, the included trials showed no significant difference in clinical signs and symptoms between intervention and control groups, differing to the work of Johansson et al. [12].

Despite the relative similarity of the study design of the randomised controlled trials (RCTs) included in the systematic review, there are always some levels of inconsistency due to variability in factors, such as treatment duration, outcomes assessed, patient age, severity of illness for need of surgery and co-morbid conditions. This is of clinical significance as plasma concentration of syndecan-1 and hyaluronic acid can vary dependant on the kidney's ability to excrete them [41]. These facts have not been reported consistently and cannot be assessed in this study. Finally, the authors were unable to find universal dosing strategies identified from official bodies for guidelines to treat EG degradation in surgery. Therefore, the dosing strategies in the RCTs were variable.

With the relatively-high level of heterogeneity indicated by I^2, these limitations highlight a real need for a set design for clinical trials to cohesively investigate protective treatments against EG degradation in surgery. Guidelines and reporting standards should be used to increase uniformity and reduced heterogeneity between RCTs, therefore max-

imising confidence, validity and comparative analysis for subsequent systematic reviews. Following is a list of suggestions for future RCTs on this topic;

- Study design: trials should be a placebo-controlled, double-blind, and a parallel design, with treatment administered pre-operatively or following the induction of anaesthesia but before the start of the surgical procedure. Time-points should be assessed at all stages of the surgical operation (pre-operative, intra-operative and post-operative) to assess trends in which the treatments affect the production of glycocalyx products.
- Patient population: RCTs should evaluate the work of Johansson study [12] to assess EG degradation in patients with greater operative stress. Mean age, concomitant medication, incidence and common co-morbidities should be collected and reported for each treatment group.
- Clinical outcomes: syndecan-1 and heparan sulphate should be used as primary markers to measure the degree of EG degradation. In addition, inflammatory markers (CRP, white blood cells) as well as capillary leakage of albumin (HGB and albumin) should be measured and correlated to identify relationships with glycocalyx shedding. Future work should use either Hedin and Hahn [42] or Hasselgren [43] technique to measure capillary leakage.

5. Conclusions

Whilst the effects of surgery are known to cause shedding of the EG, clinical surgical research into protective treatments for this structure are still in the early stages. The aim of this systematic review was to investigate treatments listed on large clinical databases to protect against EG degradation in surgery. Reviewing the pooled data from 385 patients in 8 RCTs, interventions looked to target (1) dampening the inflammatory response or (2) fluid maintenance during surgery. From these initial studies, we have seen some promising results. Methylprednisolone is shown to target the transient increase of syndecan-1 levels immediately after surgery. There is evidence that UTI can reduce the degradation of the EG with a reduction of albumin extravasation. Building from the initial findings of the included studies in this systematic review, and following the proposed suggestions for study design, the hope is that future RCTs will improve uniformity and maximise confidence for finding protective treatments for the EG in surgery.

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