RCT Evaluating Safety & Efficacy of Sodium Hyaluronate/Carboxymethylcellulose at Cesarean Delivery

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ABSTRACT:

Introduction: To determine if placement of sodium hyaluronate/carboxymethylcellulose (HA-CMC) adhesion barrier (Seprafilm®) at cesarean delivery reduces adhesion formation at subsequent cesarean delivery. We previously reported data showing no increase in short-term complications.

Methods: 753 patients were evaluated in this multicenter, randomized study. Patients undergoing primary and repeat cesarean deliveries were randomized into either HA-CMC (N=380) or no-treatment group (N=373). The location and density of adhesions (primary outcome) were assessed at their subsequent delivery using a validated tool, which has a score from 0-12. Secondary outcomes included safety and operative times. Sixty-five patients returning for a subsequent delivery from each arm were required to show a 50% reduction in adhesions.

Results: No differences in baseline characteristics, post-operative course, or incidence of complications between the groups following randomization were noted. Eighty patients from the HA-CMC group and 92 controls returned for subsequent deliveries. Adhesions in any location were reported in 75.6% of the HA-CMC group and 75.9% of the controls (P=0.99). There was no significant difference in the median adhesion score; 2 (range 0-10) for the HA-CMC group vs. 2 (range 0-8) for the control group (P=0.65). There were no significant differences in the time from incision to delivery (P=0.56). Uterine dehiscence in the next pregnancy was reported in 2 patients in HA-CMC group versus 1 in the control (P=0.60).

Conclusion: HA-CMC adhesion barrier applied at cesarean delivery does not reduce adhesion formation at the subsequent cesarean delivery. Although we did not demonstrate efficacy for improving adhesion formation, we did not identify safety concerns.

INTRODUCTION:

- The cesarean delivery rate continues to rise, resulting in an increase in adhesive disease.
- Adhesion barriers have been shown to reduce adhesion formation following other abdominal and pelvic surgery.
- No randomized studies have evaluated the safety or efficacy of adhesion barriers at the time of cesarean delivery.
- We report data from a multicenter, randomized, controlled trial to evaluating the use of sodium hyaluronate/carboxymethylcellulose (HA-CMC) (Seprafilm® Adhesion Barrier, Sanofi Biosurgery) following placement at the time of cesarean delivery.
- Short-term safety data were previously reported with no increase incidence of complications with the use of HA-CMC.

PROJECT FUNDING:

1. Investigator-Sponsored Trial Grant, Sanofi Biosurgery.
2. PhRMA Foundation Post Doctoral Fellowship in Clinical Outcomes Research Grant.
3. GCRC Grant #MO1RR10710.

NOTE: The funding organizations (including the product manufacturer) had no role in study design, data collection, analysis, or interpretation, or in the decision to publish results. The authors designed the project and funding was then sought to support its execution through investigator-sponsored grants and other available sources.

METHODS:

- A multicenter, randomized, single blinded (patient), controlled trial
- **Sites**
  - Lehigh Valley Health Network, Allentown, PA
  - Winthrop University Hospital, Mineola, NY
  - Stony Brook University Medical Center, Stony Brook, NY
- **Inclusion criteria**
  - Patients undergoing primary or repeat cesarean delivery
  - Age ≥18
- **Exclusion Criteria**
  - Planned tubal ligation
  - Infertility resulting in ≥ 2 years of treatment to achieve current pregnancy
  - Known allergy to hyaluronic acid
  - Pain score ≥5 or IV narcotic administration within two (2) hours prior to consent
  - Medical or other serious condition which will interfere with compliance and/or ability to complete study protocol
- The goal of the adhesion barrier placement was to cover the hysterotomy site, bladder flap (if created) and the midline anterior surface of the uterus. Physician training on HA-CMC placement was provided prior to the beginning of the study and at any time during the study period at their request.
- Sample size calculation: The primary endpoint of the study (adhesion formation) was performed with the following assumptions: type I error (alpha) of 0.05, a background risk of adhesion of 50% in the no treatment group, and a 25% risk of adhesion in the treated group (i.e., a 50% reduction in adhesion formation). A sample size of 65 (of patients who returned for a subsequent cesarean delivery) in each arm would be required to detect the above difference with 80% power.
- Assessment of adhesion formation: Adhesions were assessed at the time of randomization utilizing a previously validated adhesion assessment tool (Figure 1). Participating Institutions modified the Labor and Delivery medical record to begin assessing adhesions on every patient delivering at the respective institution.
- Other measures included in this analysis (incision-to-delivery time, total operative time, blood loss, etc.) were routinely collected for all patients.
- The database of enrolled patients was periodically compared to the electronic medical record from each institution to screen for patients that had returned for a subsequent delivery. Once identified, study data was abstracted from their medical record.

RESULTS:

- Patient flow diagram is shown in Figure 2.
- A total of 754 patient were randomized to Seprafilm® (n=380) or no-treatment control (n=374).
- There were no differences in baseline demographics or pre-operative characteristics at the time of randomization (Table 1).
- Of the randomized patients, 80 from the HA-CMC group and 92 controls returned for subsequent deliveries. There were no differences between the two groups with regard to maternal age, gravidy, parity, or ethnicity.
- Delivery was accomplished at a mean gestational age of 38.6 ± 1.3 weeks for the HA-CMC group versus 38.4 ± 2.0 for the control (P=0.42).
- There was similarly no difference in BMI between the two groups (32.9 ± 8.7 for HA-CMC vs. 33.0 ± 6.9 for control group, P=0.972).
- Table 2 contains data on the surgical characteristics of the patients who returned for a subsequent delivery, with no significant differences between the two groups. Notably, there was no difference in skin-to-delivery time, total operative time, or estimated blood loss.
- Table 3 contains the primary outcome (adhesion data) at the time of subsequent delivery. Adhesions in any location were reported in 75.6% of the HA-CMC group and 75.9% of the controls (P=0.99). There was no significant difference in the median adhesion score; 2 (range 0-10) for the HA-CMC group vs. 2 (range 0-8) for the control group (P=0.65).
- We arbitrarily defined "severe adhesions" as the upper quartile for the adhesion score. One third of the HA-CMC patients met the definition for severe adhesions compared to 15.5% in the control group.
- Post-operatively, hematocrits (%) were similar (30.4 ± 3.1 for HA-CMC vs. 30.0 ± 3.5 for the control, P=0.44). There was also no difference in the length of stay (days) following the subsequent delivery (median 3, range 1-9 for HA-CMC vs. median 3, range 1-5 for controls, P=0.51).

Figure 1. Adhesion Assessment Scoring

Location	None	Filmy	Dense
Bowel	0	1	2
Uterus to fascia (anterior abdominal wall)	0	1	2
Omentum to fascia (anterior abdominal wall)	0	1	2
Omentum to uterus	0	1	2
Baldder to uterus	0	1	2
Other pelvic structure	0	1	2

* Minimum total score = 0; maximum total score = 12

Adopted from Lyell et al. Obstetrics and Gynecology 2005 Aug;106(2): 275-80.

Figure 2. CONSORT Patient Flow Diagram

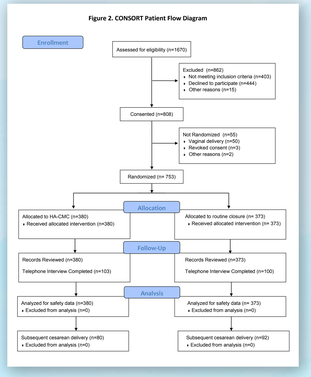

Table 1. Patient Demographics and Pre-operative Characteristics

Patient Characteristics	HA-CMC (n=380)	No Treatment (n=373)
Maternal age (years)*	30.4 ± 5.1	30.9 ± 5.3
Gravity**	2 (1-20)	2 (1-11)
Parity**	1 (0-4)	1 (0-4)
Race/Ethnicity, % (n)		
Caucasian	68.2 (259)	70.6 (264)
African-American	10.3 (39)	10.2 (38)
Asian	3.7 (14)	4.8 (18)
Latino	15.2 (59)	11.5 (43)
Other race/ethnicity	2.4 (9)	2.7 (10)
Gestational age (weeks)*	38.7 ± 1.9	38.7 ± 3.9
Body-mass index (kg/m2)*	33.3 ± 6.6	33.2 ± 7.8
Number of previous cesareans**	1 (0, 3)	1 (0, 3)
Indication for cesarean, % (n)		
Planned repeat cesarean	70.0 (266)	67.0 (250)
Non-reassuring fetal heart rate	2.6 (10)	3.0 (11)
Arrest of labor	5.5 (21)	3.2 (12)
Failed induction	1.8 (7)	3.2 (12)
Previous uterine surgery	1.8 (7)	2.4 (9)
Malpresentation	14.2 (54)	13.9 (52)
Abnormal placentation	1.3 (5)	2.7 (10)
Multiple gestation	4.5 (17)	6.7 (25)
Maternal infection	0.8 (3)	1.3 (5)
Diabetes (any), % of arm (n)	9.8 (37)	11.8 (44)
Type I	0.8 (3)	0.5 (2)
Type II	1.0 (4)	0.5 (2)
Gestational Diabetes, A1	4.5 (17)	4.8 (18)
Gestational Diabetes, A2	3.4 (13)	5.6 (21)
Pre-operative hematocrit*	34.8 ± 4.3	34.4 ± 5.0
Pre-operative WBC count*	10.3 ± 3.4	10.7 ± 4.6
Pre-operative T_{max} ** (°F)	97.8 ± 1.0	97.9 ± 0.9

* Data are presented as mean (standard deviation) and compared between groups using the student's t-test based on unequal between-group variances.

** Data are presented as median (range), and compared between groups based on the two-sample median test.

Table 2. Subsequent Delivery Surgical Characteristics

Patient Characteristics	HA-CMC (n=80)	Control (n=92)	p-Value
Urgency of cesarean, %			0.793
Scheduled	78.8	76.1	
Non-emergent	20.0	20.7	
Emergent	1.3	3.3	
Labor prior to operation, %	20.0	21.7	0.852
Rupture of membranes, %	6.3	8.7	0.579
Skin to delivery time (minutes)	8 (1-22)	8 (2-27)	0.973
Total operative time (minutes)	60 (22-112)	58 (15-123)	0.540
Diabetes (%)	15 (1.3)	32 (1.2)	0.941
Cesarean procedure type, %			
Low transverse	98.8	96.7	0.624
Classical	1.3	2.2	0.999
Estimated blood loss (ml)	800 (500-2000)	800 (600-1500)	0.745
Overall complications, % (n)	8.8 (7)	4.4 (4)	0.665
Bladder injury	0.0	0.0	-
Bowel injury	5.2 (4)	2.3 (2)	0.423
Hysterectomy	0.0	0.0	-
Intra-operative transfusion	1.3 (1)	1.1 (1)	0.999
Placenta accreta	0.0	0.0	-
Uterine rupture	0.0	0.0	-
Uterine dehiscence	2.5 (2)	1.1 (1)	0.598

Table 3. Subsequent Delivery Adhesion Data (Primary Outcome)

Adhesion Characteristics	HA-CMC (n=80)	Control (n=92)	p-Value
Adhesion score*	2 (0-10)	2 (0-8)	0.647
Any adhesion (any location), %	75.6	75.9	0.999
Bowel adhesions, %	5.2	2.3	
Uterus to fascie, %	36.4	26.7	
Omentum to fascia, %	32.5	27.9	
Omentum to uterus, %	18.2	23.3	
Bladder to uterus, %	65.4	62.1	
Other location, %	5.2	10.5	
Severe adhesions, %	33.3	15.5	0.052

* Data are presented as median (range), and compared between groups based on the two-sample median test.

DISCUSSION:

- HA-CMC adhesion barrier did not reduce the incidence of adhesions at the time of subsequent cesarean delivery.
- There were similarly no difference in operative times or the incidence of complications when HA-CMC was used compared to routine closure.
- This study is important given the frequency of cesarean delivery and the possibility of a rise in adhesion-related complications due to the historically high cesarean delivery rate.
- Before incorporating an adhesion barrier (and its associated cost) into routine practice, it is important to vigorously test its ability to achieve the desired goal.
- Our data do not support routine use of HA-CMC at the time of cesarean delivery.

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