

Role of Hyaluronic Acid Barrier Gel in Adhesion Prevention

AYESHA SAIF, NABEELA SHAMI, SHAILA ANWAR, SHAHEENA ASIF

Department of Obstetrics & Gynaecology, Lahore Medical & Dental College/GTTH, Lahore

Correspondence to Dr. Ayesha Saif, Assistant Professor Email: drayeshawasif@gmail.com Cell: 0320-1770077

ABSTRACT

Background: Adhesions after abdominal and pelvic surgery lead to increased morbidity and make the subsequent surgery difficult. Such adhesions can impair the quality of life of patients and surgical treatment is often required which is difficult, hence, adhesion prevention remains the key. To reduce the risk of adhesion formation, meticulous surgical technique is of prime importance. Historically, various agents like antibiotics, steroids, anti-inflammatory agents and barrier agents have been used without conclusive evidence. Recently, an anti-adhesion gel barrier, hyaluronic acid gel, has been introduced. Hyaluronic acid is a natural lubricant in our joints, which can contribute to adhesion prevention by mechanical separation of peritoneal surfaces.

Aim: To evaluate the effectiveness of hyaluronic acid gel in adhesion prevention and its side effects.

Methods: A multi-center prospective observational study was conducted at Ghurki Trust Teaching Hospital and Surgimed Hospital from April, 2016 to March, 2018. We selected 200 patients who presented in our hospitals by non-probability consecutive sampling technique. The patients were operated for different indications including lower segment cesarean section, total abdominal hysterectomy, ovarian cancer surgery, myomectomy, ovarian cystectomy, and laparotomy for ectopic pregnancy. Patients were informed about the benefits of hyaluronic acid gel prior to the surgery and informed consent was taken. Hyaluronic acid barrier gel was instilled at the incision line before the abdomen was closed.

Results: The mean age of our patients was 31 years (18-62) and the majority of patients were in the 21-30 years age group. 147 (73.5%) patients were operated for the first time in our study sample. Thirty three (16.5%) patients had previous one cesarean section and hence this was their second surgery. Sixteen patients (8%) had previous two cesarean sections. Of the remaining four patients, two had previous three cesarean sections and two had previous four cesarean sections. The most common indication of surgery in our study group was lower segment cesarean section i.e., 131 patients (65.5%) followed by total abdominal hysterectomy in 33 patients (16.5%). Twenty nine patients had laparotomy. One hundred and thirteen surgeries were performed electively and the remaining 87 patients had emergency surgeries. The patients were followed up on the seventh post-operative day, second follow up was via telephone after one month and third one was at the end of six months. The patients were asked about any symptoms related to adhesions (abdominal pain). The final follow-up was at subsequent surgery on the same area. We re-operated 12 patients in this 1 year period, six of them had repeat cesarean sections and three had laparotomy for endometriotic cyst excision. Three patients were re-operated for debulking surgery in advanced ovarian malignancy. We did not find any adhesions on repeat surgery in any of these patients and the previous incision site was clean, so hyaluronic acid gel was instilled again.

Conclusion: Our study indicated that no adhesions were present on repeat surgery. However, more time is required as only a few patients were re-operated in this time. More studies need to be carried out to establish the role of hyaluronic acid gel in adhesion prevention.

Keywords: Hyaluronic acid, adhesion prevention, myomectomy, laparotomy

INTRODUCTION

Fibrous bands that develop between tissues due to abrasion or handling during surgery are called adhesions^{1,4}. They are considered as internal scars that interface tissues not normally associated. Adhesions are formed by a complex process. They mostly develop after surgery when two injured surfaces are nearby. This regularly causes irritation and fibrin deposition onto the injured tissues. The fibrin at this point associates the two injured surfaces and it behaves like a paste to seal the damage and forms the band which is called "fibrinous band"¹. A group of fibrinolytic enzymes acts at this site to reduce the extent of this band and may even disintegrate it¹. In some cases, however, the production of these enzymes is affected due to injury resulting in the persistence of this fibrous band and infiltration of macrophages, fibroblasts

and blood cells¹. These cells lay down collagen and matrix into this band, hence building a permanent adhesion¹.

Adhesion formation is a common problem. Recent literature showed that more than 90% people develop adhesions after abdominal surgery and 55 to 100% people develop adhesions following pelvic surgery². Such adhesions disturb the anatomy and access at subsequent surgery on the same area. This leads to increased operative time, also the risk of iatrogenic injury to surrounding viscera increases.

Adhesions usually manifest as pain in the abdomino-pelvic area, however, patients with adhesions may not be symptomatic at all, indicating different pain threshold of patients. Adhesions can affect the normal interaction between fallopian tubes and ovary, leading to infertility in 20 to 40% of population³. Complications such as acute or sub-acute small bowel obstruction (60%), constipation and chronic pelvic pain (40%) are attributed to adhesions³.

Received on 07-08-2018

Accepted on 05-12-2018

Hence the quality of life of the patients can be severely compromised. Surgical treatment (adhesiolysis) is often required, however, adhesions commonly reform after adhesiolysis. Hence, strategies should be adopted to prevent the formation of adhesions.

Meticulous surgical technique is of paramount importance to minimize the risk of adhesion formation. This means avoiding bleeding, minimal tissue handling, proper asepsis to reduce the risk of contamination, using diathermy only when necessary and limited use of abdominal sponges and sutures. However, these efforts may not be sufficient to prevent the formation of adhesions. The risk of adhesion formation can be reduced by the use of certain products, especially, in procedures with a high risk of adhesion formation such as ovarian cystectomies, endometriotic cyst excision, fallopian tube surgery and myomectomy^{4,5}. Some products reduce the formation of adhesions by interfering with the biological processes involved in adhesion development. Others form mechanical barriers between the organs and tissues, thus providing a temporary separation after surgery³.

Historically, steroids have been used for adhesion prevention especially in fertility preserving pelvic surgery but their use is not supported by published evidence. Moreover, the use of steroids may impair the healing process and may even suppress the hypothalamic pituitary axis⁵.

Anti-histamines, antibiotics, steroids and anti-inflammatory agents have not been found to be effective in adhesion prevention⁵. The use of icodextrin, crystalloids and hyperosmotic solutions has been investigated but they failed to reduce adhesion formation⁶.

Hyaluronic acid, a main component of the connective tissue of human body, is a linear polysaccharide with disaccharide units composed of sodium D-glucuronate and N-acetyl-D-glucosamine^{6,7}. It is a transparent and a highly viscous gel. It adheres to the tissue surface and to the abdominal wall creating an anti-adhesion barrier, which keeps the adjacent tissues separated after surgery, protecting against adhesions. It is absorbed from the peritoneal cavity after seven days (the critical time of adhesion formation). Several derivatives of hyaluronic acid are commercially available.

The purpose of our study was to see the effects of hyaluronic acid barrier gel in adhesion prevention and its side effects in gynecological and obstetrics patients.

MATERIALS AND METHODS

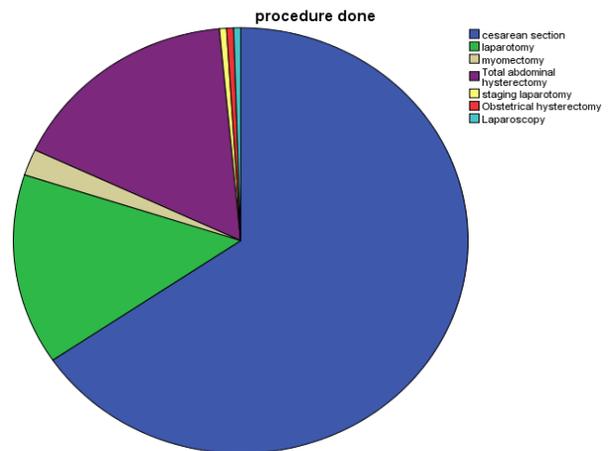
The multi-center prospective observational study was conducted from April, 2016 to March, 2018 at Ghurki Trust Teaching Hospital, Lahore, Pakistan and Surgimed Hospital, Lahore, Pakistan. The study was approved by the institutional Ethical Committee. Non-probability convenient sampling technique was used. The patients were operated for different indications including Lower segment cesarean section, Total abdominal hysterectomy, Surgery for ovarian cancer, Myomectomy and Cystectomy. All the patients were briefed about the benefits of hyaluronic acid gel prior to the surgery and informed consent was taken. 5ml of Hyaluronic acid gel barrier was instilled uniformly in the

peritoneal cavity at the operative field. The data was entered and analyzed in SPSS version 20.

RESULTS

The mean age of our patients was 31 years (18-62) and the majority of patients were in the 21-30 years age group. 147 (73.5%) patients were operated for the first time in our study sample. Thirty three (16.5%) patients had previous one cesarean section and hence this was their second surgery. Sixteen patients (8%) had previous two cesarean sections. Of the remaining four patients, two had previous three cesarean sections and two had previous four cesarean sections. The most common indication of surgery in our study group was lower segment cesarean section i.e. 131 patients (65.5%) followed by total abdominal hysterectomy in 33 patients (16.5%). Twenty nine patients had laparotomy (Fig.1). One hundred and thirteen surgeries were performed electively and the remaining 87 patients had emergency surgeries.

Fig. 1



Follow up: The patients were followed up on the seventh post-operative day, second follow up was via telephone after one month and third one was at the end of six months. The patients were asked about any symptoms related to adhesions (abdominal pain). The final follow-up was at subsequent surgery on the same area. The final follow up i.e. subsequent surgery has been carried out on twelve patients so far. Six patients had cesarean section, three had laparotomy and another three patients had de-bulking surgery for advanced ovarian malignancy. As it can be

seen in the Figure 2 and Figure 3 below, the operative field was absolutely free of adhesions; hence hyaluronic acid barrier gel was instilled again.

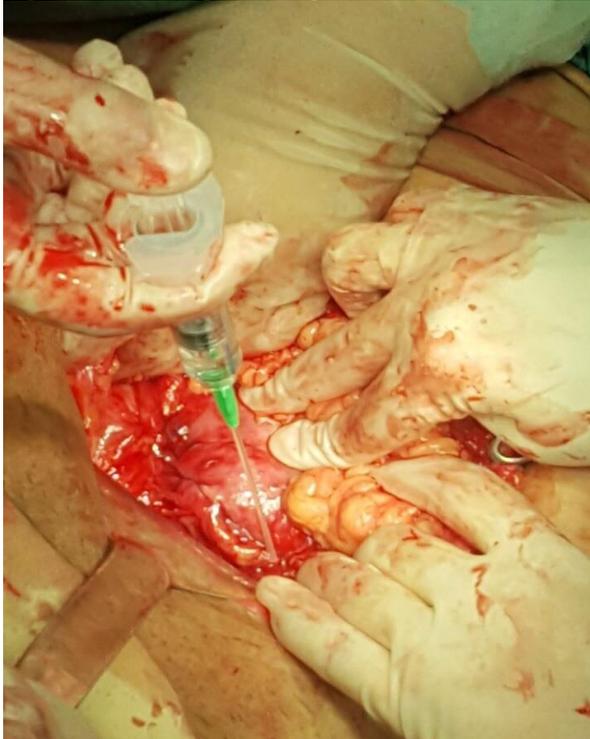
Fig. 2: Subsequent Surgery (picture was taken after opening the peritoneal cavity. no adhesions were noted)



Fig. 3: Subsequent Surgery (picture was taken after opening the peritoneal cavity. no adhesions were noted)



Fig. 4: The barrier gel is being instilled



DISCUSSION

Adhesion formation is a common problem but the different pain threshold of patients (symptomatic adhesions) and different tissue response of every patient makes it difficult to predict the extent of adhesions before surgery. Hence they are clearly seen only at repeat surgery on the same area. Adhesiolysis, although, breaks the adhesions but these adhesions tend to reform. Hence, the emphasis should be made on preventing their formation. Meticulous surgical technique along with the use of adhesion reducing agents help in minimising the adhesion formation. Many agents have been used previously to meet this end but have not been effective. This has led to skepticism about the use of newer agents.

This small study reflects upon the advantages of hyaluronic acid barrier gel in prevention of adhesions. While conducting this study, when patients were briefed about the benefits of this gel, none of our patients were reluctant to give consent for its use indicating its acceptability.

Our study indicated that no adhesions were present on repeat surgery but since only 12 patients are re-operated so far, which is a limitation of our study, we need more time so that more patients can be re-operated and confirmation of its effectiveness can be made. Our patients did not report any side effects related to adhesions but adhesions are not always symptomatic, moreover, the pain threshold of the patients varies.

Another major concern is its high cost. Pakistan is a developing country and majority of our population belongs to lower socio-economic strata of the society, and basic necessities of life are not available to a wide majority of patients, so a single 3ml injection which is expensive is not easily affordable to the population at mass level. Hence, to avoid its confinement to only upper social class, its price issue needs to be addressed. One way of addressing this issue is to consider its local production.

The gel can provide a breakthrough in treatment of patients with endometriosis, recurrent ovarian cysts, malignancies and in obstetrics where repeated surgeries are more common. Incorporating this gel in routine use can reduce the operative time, shorten the hospital stay, reduce the post-operative morbidity and even improve the quality of life of patients.

Conflict interest: None

REFERENCES

1. Di Zerega AB, Gere; Campeau, Joseph (2001). "Peritoneal Repair and Post-Surgical Adhesion Formation"(PDF). *Human Reproduction Update*. 7(6): 547-555. doi:10.1093/humupd/7.6.547. Retrieved 22 May, 2014
2. Liakakos, T; Thomakos, N; Fine, PM; Dervenis, C; Young, RL (2001). "Peritoneal Adhesions: Etiology, Pathophysiology, and Clinical Significance. Recent Advances in Prevention and Management". *Digestive surgery*. 18 (4): 260-73. doi:10.1159/000050149. PMID 11528133
3. Trew G. Postoperative Adhesions and Their Prevention. *Rev Gynaecol Perinatal Pract*. 2006;6(1-2):47-56. doi: 10.1016/j.rigapp.2006.02.001.
4. Diamond MP, Wexner SD, diZerega GS et al (2012). *Adhesion Prevention and Reduction: Current Status and*

- Future Recommendations of a Multinational-Interdisciplinary Consensus Conference. *SurgInnov* 17:183-188
5. De Wilde RL et al;(2012)."Prevention of Adhesions in Gynaecological Surgery: the 2012, European Field Guideline"
 6. Metwally M, Watson A, Lilford R, Vandekerckhove P. Fluid and Pharmacological Agents for Adhesion Prevention After Gynaecological Surgery. *Cochrane Database Syst Rev* 2006;(2):CD001298
 7. Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Hyaluronan Gel for Adhesion Prevention in Laparoscopy and Hysteroscopy: a Systematic Review and Meta. Efficacy of Auto-Crosslinked Analysis of Randomized Controlled Trials. *Eur J Obstet Gynecol Reprod Biol.* 2012;160:1-5
 8. Trew G, Pistofidis G, Pados G, Lower A, Mettle L, Wallwiener D, et al. Gynaecological Endoscopy Evaluation of 4% Icodextrin Solution: a European, Multicentre, Double-Blind, Randomized Study of the Efficacy and Safety in the Reduction of De Novo Adhesions After Laparoscopic Gynaecological Surgery. *Hum Reprod*2011; 26:2015-27.
 9. "Adhesion Prevention: A Standard of Care". American Society for Reproductive Medicine. Medical Association Communications. Retrieved 23 May 2014
 10. Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, et al. Barrier Agents for Adhesion Prevention After Gynaecological Surgery. *Cochrane Database Syst Rev* 2008;(2):CD000475
 11. Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Efficacy of Auto-CrossLinked Hyaluronan Gel for Adhesion Prevention in Laparoscopy and Hysteroscopy: ASystematic Review and Meta-Analysis of Randomized Controlled Trials. *Eur J Obstet Gynecol Reprod Biol* 2012;160:1-5.
 12. Allbright CM, Rouse DJ. Adhesion Barriers at Cesarean Delivery: Advertising Compared with the Evidence. *ObstetGynecol*2011; 118:157-60.
 13. Sawada T, Nishizawa H, Nishio E, Kadowaki M (2000) Postoperative Adhesion Prevention with an Oxidized Regenerated Cellulose Adhesion Barrier InInfertile Women. *J Reprod Med* 45:387-389
 14. M. Riccio, B. Battistonetal. Efficiency of Hyaloglidein the Prevention of the Recurrence of Adhesions After Tenolysis of Flexor Tendons in Zone II :A Randomized, Controlled, Multicentre Clinical Trial. *The Journal of Hand Surgery (European Volume, 2010)* 35e: 2: 130-138
 15. van der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MMPJ, Schaapveld M, van Goor H (2000). Morbidity and Mortality of Inadvertent Enterotomy During Adhesiotomy. *Br J Surg* 87:467-471
 16. Swank DJ, Swank-Bordewijk SCG, Hop WCJ, van Erp WFM, Janssen IMC, Bonjer HJ, Jeekel J (2003). Laparoscopic Adhesiolysisin Patients with Chronic Abdominal Pain: A Blinded Randomized Controlled Multi-centre Trial. *Lancet* 361:1247-1251
 17. Sawada T, Nishizawa H, Nishio E, Kadowaki M (2000) Postoperative Adhesion Prevention with an Oxidized Regenerated Cellulose Adhesion Barrier in Infertile Women. *J Reprod Med*45:387-389
 18. Diamonda T; The Seprafilm Adhesion Study Group (1996) Reduction of Adhesions After Uterine Myomectomy by Seprafilm Membrane (HAL-F): A Blinded, Prospective, Randomized, Multicenter Clinical Study. *Fertil Steril* 66:904-910.
 19. Mettler L, Hucke J, Bojahr B, Tinneberg HR, Leyland N, Avelar R. A safety and efficacy study of a resorbable hydrogel for reduction of post-operative adhesions following myomectomy. *Hum Reprod.* 2008;23: 1093-100.
 20. Sileri P, Sthory R, McVeigh E, Child T, Cunningham C, Mortensen NJ, et al. Adhesions are common and costly after open pouch surgery. *J Gastrointest Surg.* 2008;12:1239-45.
 21. Fatusic Z, Hudic I. Incidence of post-operative adhesions following Misgav Ladach caesarean section—a comparative study. *J Matern Fetal Neonat Med.* 2009; 22:157-60.
 22. Schreinemacher MH, ten Broek RP, Bakkum EA, van Goor H, Bouvy ND. Adhesion awareness: a national survey of surgeons. *World J Surg.* 2010;34:2805-12
 23. Kumar S, Wong PF, Leaper DJ. Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. *Cochrane Database Syst Rev.* 2009;CD005080
 24. Hirschelmann A, Wallwiener CW, Wallwiener M, Weyhe D, Tchartchian G, Hackethal A, De Wilde RL (2012) Is patient education about adhesions a requirement in abdominopelvic surgery? *Geburtshilfe Frauenheilkd* 72:299-304
 25. Ten Broek RP, Kok-Krant N, Verhoeve HR, van Goor H, Bakkum EA. Efficacy of polyethylene glycol adhesion barrier after gynecological laparoscopic surgery: Results of a randomized controlled pilot study. *GynecolSurg*2012; 9: 29-35.
 26. Kim TH, Kim JS, Lee HH, Nam KH, Lee KH, Lee JJ. Prevention of vesicouterine adhesion after cesarean with Interceed. *Korean Society of Fetal Medicine, 10th Annual Congress ofPerinatal Society of Australia & New Zealand;* 3-6 Apl 2006; Perth, Australia.