

Summary of independent studies on Celox Hemostats.

Introduction and Executive Summary

This summary assembles the known published independent testing on Celox haemostats for information to review the Celox technology. Scope: independent published or in press journal articles; current marketed variants i.e. Celox granules, Celox-A granules in applicator, Celox Gauze and Celox Rapid Gauze. Note: in all product forms the “active” chitosan component, the Celox granules, is identical, the differences are in presentation and quantity.

The results show that Celox has been subject of extensive clinical, laboratory performance and safety testing with consistently positive results, including:

- Two published journal articles and a technique note on human clinical use in Afghanistan.
 - Treatment is effective and safe.
- Three peer-reviewed papers on emergency use cases in hospital.
 - Arrests life-threatening, coagulopathic bleeding.
- **16** independent laboratory studies on Celox Gauze and Celox Granules excellent performance throughout.

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Published Clinical Use

Celox has been used since 2006 in military and civilian emergency medicine and in hospitals. The results in conflict and in hospital have been published in peer-reviewed journals and are listed below. The summary is split into:

- **Three clinical papers relating to military use in Afghanistan^{1,2,3}.**
- **Three clinical papers on hospital use to arrest uncontrollable emergency bleeding^{4,5,6}.**

Military publications:

- **Successful use in life-threatening bleeding.**
- **Gunshot, blast and other injuries.**
- **Afghanistan conflict & civilian EMS settings.**
- **No recorded complications.**

(1) Celox (chitosan) for haemostasis in massive bleeding: experience in Afghanistan¹. Published in European Journal of Emergency Medicine

- **21 Gunshot wound cases (15 life-threatening).**
- **Bleeding controlled successfully in all cases with Celox.**
- **Used where tourniquet did not control bleeding.**

The article reports use in ISAF in 2008 at Role 2 by Italian medical team to treat GSW to lower limb (13), upper limb (4), shoulders (3) and neck (1). Tourniquets had been used in 15/17 limb injuries but had not stopped the bleeding. There was no reported pain and no changes to the tissue surrounding the injuries were noted.



GSW entry and exit wounds treated with Celox. Image from conference poster of same study⁷.

(2) Field experience with a chitosan-based haemostatic dressing². Published in Medical Corps International Forum.

- **Celox Gauze used on GSW, blast, crush and other injuries.**
- **Arrested bleeding in 6/7 cases.**
- **No leakage no re-bleeding in evacuation.**

The article describes cases from a Dutch team at a Role 2E facility in Afghanistan in 2010 and domestic civilian Air Ambulance use. Injury sites were lower limb , pelvic girdle, side of neck and ears and nose. Injury cause was IED blast, GSW, crush, sharp amputation, RTA and fall from height. In 6 out of 7 cases Celox was successfully used to stop bleeding. Treatment in one case, the fall with blood coming from ear and nose, was not successful; this was thought to be because the product could not be brought close to the source of the bleeding.

(3) A pre-hospital technique for controlling haemorrhage from traumatic perineal and high amputation injuries³. *Journal of the Royal Army Medical Corps*

This journal technique note describes a technique for using Celox and emergency bandage to treat IED blast injuries. It states: **“this technique has been used to good effect on recent deployments in the MERT helicopter by the second author.”**

Hospital use publications:

The following papers are case reports of hospital use of Celox and a clinical study in wound debridement. They include product use off-label in emergencies.

Celox Gauze or Celox was used to arrest bleeding in:

- **Uncontrollable sternal bleeding with severe coagulation problems (post-ECMO).**
- **Life-threatening bleeding in emergency cardiac cases.**
- **Uncontrollable post-partum hemorrhage^c.**

Article	Key points
<p>(1) Successful use of a military haemostatic agent in patients undergoing extracorporeal circulatory assistance and delayed sternal closure⁴. <i>In Interactive CardioVascular and Thoracic Surgery.</i></p>	<ul style="list-style-type: none"> • Two cardiac patients post-ECMO. • Uncontrolled sternal bleeding. • Reduced platelet count and circulating heparin. • Blood products and topical hemostatics failed. • Celox Gauze used to control bleeding.
<p>(2) A New Hemostatic Agent: Initial Life-Saving Experience with Celox (Chitosan) in Cardiothoracic Surgery⁵. <i>The Annals of Thoracic Surgery</i></p>	<ul style="list-style-type: none"> • Two cardio-thoracic cases. • One post-surgery bleed, one stab injury • Vessels treated: left anterior descending coronary artery (case 1); extensive arterial bleeding from pleura at apex of thoracic cavity (stab case). • Both cases successfully stopped with Celox.
<p>(3) Postpartum hemorrhage: use of hemostatic combat gauze⁶. <i>American Journal of Obstetrics & Gynecology.</i></p>	<ul style="list-style-type: none"> • Uncontrollable post-partum bleeding in elective caesarean. • Repeated episodes of bleeding. • Oxytocin, sulpostrone, re-laparotomy and suturing unsuccessful. • Packed Celox Gauze and stopped bleeding.

Systematic Review of Hemostatics

Pre-hospital haemostatic dressings: A systematic review⁸. *Injury – International Journal of care of the injured.*

One systematic review focuses on pre-hospital haemostats. The review was part of the decision-making process that led the UK MoD to choose Celox Gauze over Combat Gauze. This article reviewed the clinical and pre-clinical evidence up to 2009, including 37 pre-clinical papers after excluding non-lethal models and haemostats that were not suitable for operational deployment. The authors conclude that the “newer” agents including Celox showed promise of outperforming the standards of the time (Hemcon and Quikclot). They also considered safety and ease of removal. “Celox also appears to be effective and safe: it is now also available as a gauze roll.”

- **Finds Celox effective in arterial and mixed hemorrhage.**
- **Outperforms Hemcon and Quikclot ACS+.**
- **Safe.**

Independent Laboratory Studies – Celox Gauze

Celox Gauze has been tested in three independent laboratory publications^{9,10,11}, comparing performance against other Gauze hemostats.

- **Consistent high performance against Combat Gauze and Chitogauze (fig 1, table 1).**
- **In recent Navy study⁹, Celox Gauze had significantly less blood loss than Combat Gauze at “platinum” 10 minute point and similar trends throughout test.**

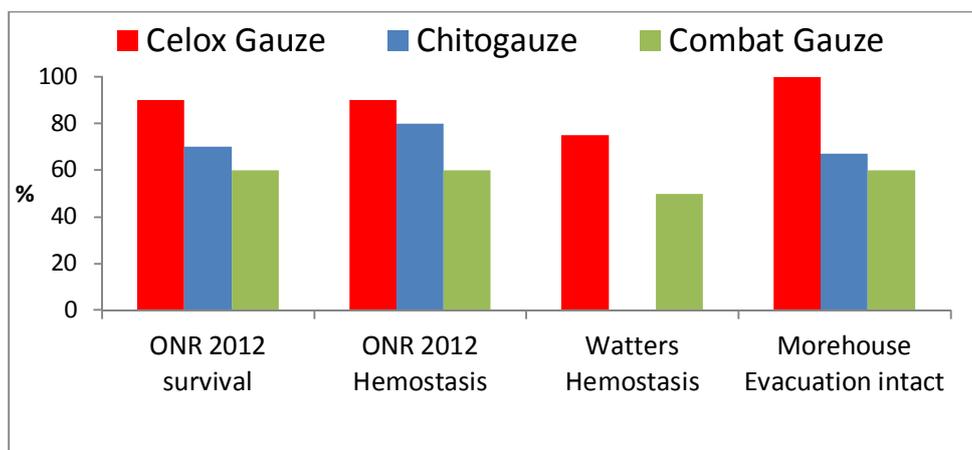


Figure 1: key results of comparative testing for Celox Gauze.

<i>study</i>	US Navy 2012 ⁹		Watters 2011 ¹⁰	Morehouse 2010 ¹¹
<i>Model</i>	Femoral artery 6 mm punch.		“care under fire” femoral artery 6 mm punch, no compression after packing.	Evacuation model.
<i>sample size</i>	10 per group.		8 per group	variable, 2-10 trials.
<i>comment</i>	No primary outcome defined: survival and hemostasis reported here.		Muscle bellies left intact for self-compression.	only 2 trials for Celox. Not peer reviewed.
<i>primary measure</i>	Survival	Hemostasis	Hemostasis	Hemostasis after evacuation
Celox Gauze	90 %	90 %	75 %	100 %*
Chitogauze	70 %	80 %	-	67 %
Combat Gauze	60 %	60 %	50 %	60 %

Table 1: Summary of comparative results: Celox Gauze, Combat Gauze and Chitogauze.

Articles

(1) Comparison of novel hemostatic gauzes to Quikclot Combat Gauze in a standardized swine model of uncontrolled hemorrhage⁹. *ONR report.*

- **Celox blood loss significantly less than Combat Gauze at “platinum 10 minute” point.**
- **Celox Gauze achieved 90 % survival, while other dressings recorded 50 – 70 %.**
- **Celox Gauze had lowest value for blood loss**
- **Celox Gauze had highest eventual hemostasis.**

(2) Advanced hemostatic dressings are not superior to gauze for care under fire scenarios¹⁰. *Journal of Trauma.*

This study uses a model of a wound with no compression applied, intended to simulate care under fire. In the study plain gauze achieved higher hemostasis than hemostatic dressings. In the associated conference discussion, the author put this down to the level of experience of the person packing. However, the intact muscle bellies provide some inherent compression.

- **Celox Gauze 75 % hemostasis compared to Combat Gauze 50 %.**
- **Total blood 205 ml for Celox Gauze, 260 ml plain gauze, 374 ml for Combat Gauze.**
- **No inflammation, necrosis, or deposition of dressing particles in vessel walls.**
- **No difference in histologic or ultrastructural findings between dressings.**

(3) Hemorrhage control agents: a comparative analysis¹¹. *Defence Global*

A model of casualty evacuation. Medics were given a fixed amount of haemostatic product to treat wounds and carry the swine model over a course. Outcome: hemostasis at final checkpoint. The publication is not a peer-reviewed journal and it is not clear why Celox only had two trials; no failures were recorded with Celox Gauze.

- **Celox Gauze 100 % (2/2) successful trials. Combat Gauze 6/10 (60%) trials, Chitogauze 4/6 (67%).**

A further study has been carried out on Celox Rapid gauze, comparing it to Combat Gauze in the model of care under fire.

(4) Chitosan based advanced hemostatic dressing is associated with decreased blood loss in a swine uncontrolled hemorrhage model¹². *Submitted to American Journal of Surgery. First presented at Region X Committee on Trauma annual meeting, Olympia, Washington, 2011.*

Model of care under fire similar to Watters 2011, above. In this case they compared Celox Rapid with Combat Gauze and standard gauze. The model does not remove muscle bellies, allowing some “inherent” compression.

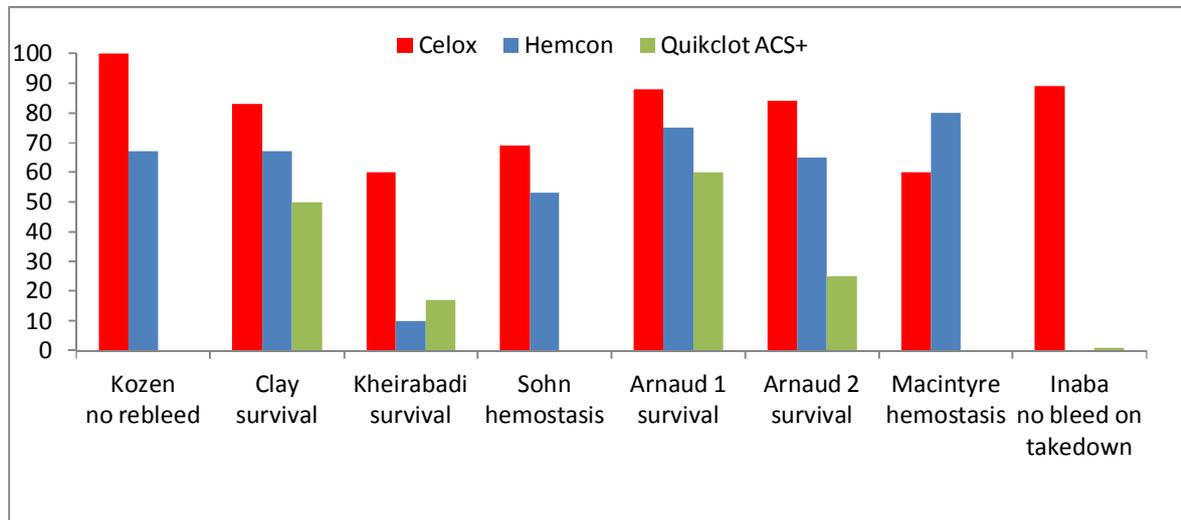
- **Celox Rapid Gauze significantly reduced blood loss compared to Combat Gauze ($p= 0.05$).**
- **Hemostasis in 12/12 for Celox Rapid (10/12 for Combat Gauze).**
- **Significantly faster packing time for Celox Rapid compared to Combat Gauze ($p=0.01$).**

Celox (granules) studies

There have been twelve independent published studies on Celox. Most of these included Hemcon or ACS+ as comparators.

Statistically significant findings include:

1. Zero re-bleeds with Celox, significantly less than Hemcon / QC ($p=0.049$)¹³.
2. 100 % survival, $p=0.049$ significantly greater than Hemcon, /QC¹³.
3. Celox had significantly higher survival compared to Hemcon ($p < 0.05$)¹⁴ (unable to compare ACS due to poor performance).
4. Significantly ($p < 0.05$) lower blood loss than Hemcon¹⁴.
5. Celox in group of products with highest survival ($p < 0.01$) and lowest re-bleed ($p < 0.005$)¹⁵.
6. Statistically superior resistance to re-bleed as blood pressure deliberately increased after clot formed ($p = 0.008$)¹⁷.
7. Significantly better hemostasis in presence of warfarin ($p < 0.001$) compared to control¹⁸.
8. Significantly improves hemostasis in hypothermic bleeding ($p < 0.01$) compared to gauze control¹⁸.



Summary of Celox studies comparative with Hemcon and/or ACS+:

<u>Study</u>	Description	sample size per group	primary measure	Celox	Hemcon	ACS+
Kozen ¹³	Femoral artery and vein sever.	12	no re-bleed	100	67	-
Clay ¹⁹	6 mm punches to femoral artery and vein.	6	Survival	83	67	50
Kheira-badi ¹⁴	Femoral artery 6 mm punch. ACS stopped due to high failure rate.	10 (6 for ACS)	survival	60	10	17
Sohn ²⁰	Goat femoral artery model. Used both sides, measured at 2, 4 minutes only.	32-55	hemo-stasis, 4 min.	69	53	-
Arnaud 1 ¹⁵	Femoral artery and vein sever.	8	survival	88*	75*	60~
Arnaud 2 ¹⁶	4 mm punch, femoral artery. Hemcon stopped due to high fail rate.	8 (4 for Hemcon)	survival	84	65~	25
Macintyre ²¹	Forelimb injury, model of reducing tourniquet time.	10	hemostasis	60	80	-
Inaba ²²	Liver injury damage control model.	11	no rebleed on removal	89	-	0

* : figures reported in (ref).
 ~ : read from graph in article.

Articles: models of arterial or mixed hemostasis

(1) An alternative hemostatic dressing: comparison of Celox, Hemcon and Quikclot¹³. *Journal of Academic Emergency Medicine.*

A groin transaction of femoral vessels with 3 minutes free bleeding. Five minute compression then covered with field compression dressing. Celox was easily removed, residual material easily washed from the wound with simple saline lavage.

- **100 % success, zero re-bleeds (p<0.001).**
- **Significant reduction in re-bleed compared to other hemostats (p=0.049).**
- **100 % survival, (others 50 – 92%) (p = 0.018 compared to gauze, p=0.049 compared to others).**

(2) Comparison of new hemostatic granules / powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine¹⁴. *Journal of Trauma*

Compared “new” haemostats: Celox, SQR and WoundStat to the standards – Hemcon and QuikClot ACS+. The “new” products outperformed the Hemcon control (ACS+ failed in 5/6 cases and was stopped). However SQR and WoundStat were difficult to remove and SQR caused very high local temperature. Celox elicited more histological damage than HC or ACS+ in this model, but less than SQR.

- **Celox had significantly higher survival (6/10) compared to Hemcon (p < 0.05).**
- **Significantly (p < 0.05) lower blood loss than Hemcon.**
- **Removal “relatively easy”.**
- **No occlusion of distal vessels, no pro-thrombotic effect.**

(3) Comparison of 10 hemostatic dressings in a groin transection model in swine¹⁵. *Journal of Trauma*

- **Celox in group of products with highest survival (p<0.01).**
- **Celox, Quikclot ACS, X-Sponge and Woundstat were superior to others including Hemcon, Chitoflex, in blood loss (p<0.05) and re-bleeding (p< 0.005).**
- **Refringent material attached to connective tissue, but no deposition in vessels that could have disrupted endothelium.**

(4) Comparison of 10 hemostatic dressings in a groin puncture model in swine¹⁶. *Journal of Vascular Surgery*

Similar test to paper above, with different injury.

- **Celox in group of products significantly outperforming Hemcon and others (p<0.01).**
- **Celox, Quikclot ACS, X-Sponge and Woundstat were superior to others including Hemcon, Chitoflex for post-treatment blood loss (p<0.001).**

(5) Comparative testing of new hemostatic agents in a swine model of extremity arterial and venous hemorrhage¹⁹. *Military Medicine*.

Tested Celox, Hemcon, QuikClot ACS and Woundstat. 6 mm punch on femoral artery and vein.

- **Celox 83 % survival, compared to Hemcon (67%), QuikClot ACS+ (50%), Woundstat (100%).**

(6) The effects of BleedArrest, Celox and TraumaDex in Hemorrhage control in a porcine model²³. *Journal of Surgical Research*.

Transected femoral artery and vein. One minute free bleed. Main outcome measure: blood loss after 35 minutes.

- **Celox significantly reduced blood loss (p=0.01) compared to standard gauze.**
- **“clinically superior to Bleedarrest and Traumadex.”**
- **No obvious signs of tissue damage**

(7) Efficacy of Three Topical Hemostatic Agents Applied by Medics in a Lethal Groin Injury Model²⁰. *Journal of Surgical Research*.

Model using goat femoral artery. Tested two wounds per animal. Tested Chitoflex, Hemcon and Celox. Chitoflex 76 % success at 4 minutes, Celox 69 %, Hemcon 53 %.

Studies of specific aspects of performance

(1) Celox can withstand increasing blood pressure without re-bleeding¹⁷. *American Association of Nurse Anesthetists*.

- **Celox stopped bleeding and maintained control as blood pressure deliberately increased to > 160 mm Hg systolic.**
- **Statistically superior compared to standard dressing in preventing re-bleed (p = 0.008 for MAP).**

(2) Hemostatic dressings reduce tourniquet time²¹. *American Surgeon*

A model using swine forelimb with an open wound model. Applied tourniquet, then hemostatic then assessed bleeding after removing tourniquet. Plain gauze failed in all cases. Celox maintained hemostasis in 6/10, Quikclot 8/10, Actcel 9/10 and Hemcon 10/10. All showed ability to reduce tourniquet time.

(3) Celox effective on hypothermic bleeding and warfarinised blood¹⁸. *Turkish Journal of trauma and Emergency Surgery*.

Found Celox to be equally effective in warfarinised bleeding and hypothermic bleeding, using a rat model of hemostasis.

(4) Celox used to pack liver as a damage control measure, measuring re-bleed after take-down²². *Journal of Trauma*

The study tested possible use of hemostatics to pack liver injury to control intracorporeal bleeding as part of a damage control approach. Outcome: recurrence of bleeding after pack removal (take-down at 48 hours).

- Celox and QuikClot significantly reduced blood loss in the 10 minutes after packing.
- At take-down 1 of 9 animals with Celox needed re-packing for bleeding. All animals treated with QuikClot or standard gauze required re-packing ($p < 0.001$).
- Celox provided durable control, allowing pack removal at time of take-back surgery for liver injury.
- No difference in injury site response, thickness of necrotic layer.

Celox-A granules in applicator.

Comparison of Celox-A, Chitoflex, Woundstat and Combat Gauze hemostatic agents versus standard gauze dressing in control of hemorrhage in a swine model of penetrating trauma²⁴.
Academic Emergency Medicine.

Penetrating narrow injury model.

- **Celox-A achieved 100 % immediate hemostasis.**
- **Significantly better hemostasis ($p < 0.002$), survival ($p < 0.01$), compared to Woundstat.**
- **Consistently ranked first for hemostasis, absence of re-bleeding and survival, against Combat Gauze, Chitoflex, Woundstat, plain gauze.**

Note: Excluded Studies

“Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine.”
Kheirabadi et al published in J Trauma 2009. This study tested a prototype version of Celox that was never commercialised (Celox-D, dissolvable bag) and is not included for that reason.

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