European Surgical Research

Eur Surg Res 2020;61:51–61
DOI: 10.1159/000509876
Received: June 1, 2020
Accepted: July 1, 2020
Published online: September 23, 2020

Review

Four-Factor Prothrombin Complex Concentrate: An Indispensable Adjunct in Coagulopathy of Trauma Management – A Comparative Review of the Literature over 2 Decades

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Keywords
Coagulopathy · Trauma · Prothrombin complex concentrate · Fresh-frozen plasma · Damage control resuscitation

Abstract
Background: Damage control resuscitation forms the cornerstone of management in trauma surgery. Several blood products have been widely used for preoperative transfusions prior to emergency surgeries and for hemorrhage control in trauma. Prothrombin complex concentrate (PCC) is now being introduced as an essential component of damage control resuscitation. ***Summary:*** We did a comparative descriptive analysis of several single and multi-institutional clinical trials and retrospective cohort studies. The primary focus of these studies was a comparison between PCC and other transfusion modalities including recombinant factor VIIa, fresh-frozen plasma, and fibrinogen based on several vital parameters. The parameters included rapid international normalized ratio reversal, hospital length of stay, cost-effectiveness, mortality rate, and rate of thromboembolic complications. ***Key Points:*** Although still awaiting its approval from the FDA for use in traumatic coagulopathy, 4-factor PCC has shown far more convincing results in contrast to former transfusion modalities, even 3-factor PCC. However, more prospective extensive clinical trials on national levels are needed to compare its effectiveness to 3-factor PCC and gather promising recognition in the trauma care fraternity.

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Introduction

Trauma is the leading cause of mortality in people aged 1–44 years in the USA [1]. Thirty percent of deaths in trauma are attributable to hemorrhage. Extensive analysis of studies has revealed exsanguinating hemorrhage as the most common preventable cause of death whose management has been a prime subject of discussion among the experts [2]. Twenty-five percent of patients with severe traumatic hemorrhage have deranged international normalized ratio (INR) on presentation, the consequences being an increase in blood transfusion products, morbidity, and mortality [3, 4]. This "trauma-induced coagulopathy" is described as a combination of hypothermia and depletion of coagulation factors occurring secondary to blood loss/hemodilution. On a molecular basis, it is manifested by activation of protein C, consequent inactivation of factors V and VIII, and inactivation of plasminogen activator inhibitor-1 leading to inhibition of fibrinolysis [5].

Since the introduction of trauma-induced coagulopathy, revolutionary changing patterns have been observed during the management of trauma patients. A better understanding of its pathophysiology has allowed the surgeons to follow a more goal-directed approach while managing traumatic hemorrhage with early coagulation factor replacements. This is defined as "damage control resuscitation," which includes permissive hypotension, reduction of crystalloid use, increasing the use of hypertonic saline, the utilization of blood products such as fresh-frozen plasma (FFP), cryoprecipitate and platelets, and recombinant coagulation factors concentrated in drug form. One of the largest clinical trials involving severely injured trauma patients (PROPRR) suggested the early administration of plasma, packed RBC, and FFP in a 1:1:1 ratio, and showed that this modality can lead to more hemostasis and fewer exsanguination-related death in the first 24 h [6]. The drugs gaining popularity in coagulopathy of trauma (COT) management were recombinant factor VIIa (rFVIIa), tranexamic acid (TXA), 3-factor prothrombin complex concentrate (3-PCC), and 4-factor PCC (4-PCC). Although still awaiting its approval by the FDA for use in traumatic coagulopathy, PCC has recently become increasingly popular. Various single as well as multi-institutional trials are being conducted globally highlighting the pivotal endpoints and weighing the risks and benefits of its use in trauma management. The results are promising and thus promoting the use of PCC over other agents such as rFVIIa and FFP.

The questions under review in our article are the following: Is PCC an effective modality of therapy in patients with COT, based upon its efficacy, cost-effectiveness, and safety profiles? Is PCC comparatively more efficacious when compared with current therapies of COT? Does 4-PCC have a better therapeutic profile when compared with 3-PCC?

Pharmacology of PCC

What Is PCC? PCC is a purified, heat-treated, nano-filtered, preservative-free, lyophilized inactivated 4-factor concentrate prepared from human plasma obtained from subjects. Besides factor II, VII, IX, and X, it also contains human albumin, sodium chloride, sodium citrate, heparin and antithrombin III – the latter 2 added to prevent the risk of thrombosis [7]. Dosage: 50 units/kg, intravenous [8].

Half-Life. The median terminal half-life is 59.7 h for factor II, 4.2 h for factor VII, 16.7 h for factor IX, and is 30.7 h for factor X [9]. PCC is stored at room temperature.

Forms of PCC. Two forms of PCC are obtainable for use, namely 3-PCC and 4-PCC. Both forms contain vitamin K-dependent coagulation factors (factors II, VII, IX, and X), the difference being that 4-PCC contains a higher amount of factor VII in addition to anticoagulation proteins (protein C, protein S, antithrombin, and heparin) [10].

Side Effects. Headache, nausea, vomiting, arthralgia, hypotension, and rarely thromboembolic (TE) events including stroke, pulmonary embolism, and deep vein thrombosis have been reported with PCC use [11, 12].

Absolute Contraindications. Anaphylactic or severe systemic reaction to PCC or any of its components, disseminated intravascular coagulation, and heparin-induced thrombocytopenia [13].

Relative Contraindications. Prior TE events including cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease, or myocardial infarction within the last 3 months [13].

FDA Approval

FDA first approved PCC for the treatment of hemophilia B. Later in 2013, nonactivated 4-PCC received FDA approval for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients needing an urgent surgery or other invasive procedures, and for the urgent reversal of warfarin therapy in adult patients with acute major bleeding [13]. However, it is still awaiting FDA approval for its use in trauma-induced coagulopathy.

PCC versus Recombinant Human Coagulation Factors

Since the advent of the concept of damage control resuscitation, there has been an ever-increasing effort to introduce drugs that can be used to effectively manage COT of which rVIIa was the first one. Its administration resulted in the control of hemostasis and a reduction in transfusion requirements and mortality rate in hemorrhagic patients, along with improvement of hematologic parameters [12, 14]. The advancements on this topic resulted in the use of FFP and then PCC, and this has led to the comparison of factor VIIa versus FFP and PCC in terms of safety, efficacy, cost-effectiveness, and dosage regimens. Table 1 summarizes the studies conducted for comparison of 3-PCC and recombinant human coagulation factors and their primary and secondary outcomes.

Sarode et al. [15] evaluated the effect of factor VIIa + PCC cocktail for patients with intracranial hemorrhage who were previously on warfarin. They introduced a "Trauma Coumadin Protocol (TCP)" which is a specialized combination of rFVII combined with concurrent intravenous vitamin K injection and studied their effects on warfarin reversal. The pre-TCP median values of coagulation factors II, VII, IX, and X were 28, 21, 45, and 20%, respectively. Post-TCP median values increased to 144, 417, 102, and 143%, respectively. In addition, the median TCP INR value significantly reduced back to normal post-therapy value.

In another trial, Safaoui et al. [16] reported that factor VIIa is not cost-effective in contrast to PCC and requires repeated dosage unless given with vitamin K and FFP, which can result in unnecessary delay in patients of traumatic intracranial hemorrhage who were previously on warfarin and require emergency surgery. PCC also demonstrated rapid INR reversal comparatively.

Joseph et al. [17], in a clinical trial of traumatic brain injury patients for comparison of PCC versus rFVIIa, reported that the PCC group had a decreased need for packed RBC and FFP transfusion, a reduction in mortality rate ($p = 0.02$), and decreased treatment charges per patient ($p < 0.01$) compared to the rFVIIa cluster. One patient who received rFVIIa died from TE complication in comparison to no patients in the PCC group. There was no statistically significant difference between the craniotomy rates ($p = 0.1$), mean time to intervention ($p = 0.9$), functional outcome calculated by GCS ($p = 0.9$), and hospital length of stay (LOS) among the PCC and rFVIIa groups, respectively. They also reported an annual rise in the use of PCC over rFVIIa as the treatment of choice over the period 2007 to 2010.

Dickneite et al. [18] compared the efficacy of PCC to factor VIIa in a porcine trauma model and reported that time to hemostasis achieved was much shorter in PCC than factor VIIa (35

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Table 1. Comparison of PCC and recombinant human coagulation factors

Clinical study	Intervention/ comparison group	Sample size, *n*	Mean INR correction	INR correction time, min	Mortality rate, %	TE events, *n*	Cost comparison, USD
Sarode et al. [15], 2012	3-PCC + rFVIIa	46	3.4 to 1.0	–	–	2	–
Safaoui et al. [16], 2009	3-PCC vs. rFVIIa	28	5.1 to 1.9*	13.5 min	35 (3-PCC)	0	1,800 vs. 7,600
Joseph et al. [17], 2013	3-PCC vs. rFVIIa	85	0.7 vs. 0.39**	394 vs. 1,050 min*	47 vs. 67*	0 vs. 1**	1,007 vs. 5,757*

* $p < 0.05$; ** $p > 0.05$.

Table 2. Comparison of 3-PCC +/– FFP and FFP alone (human studies)

Clinical study	Sample size, *n*	Correction of INR, min		Hospital LOS, days		TE complications, %		Mortality, %		Cost of therapy, USD	
		3-PCC +/– FFP	FFP alone	3-PCC +/– FFP	FFP alone	3-PCC +/– FFP	FFP alone	3-PCC +/– FFP	FFP alone	3-PCC +/– FFP	FFP alone
Joseph et al. [20], 2014	252	394**	1,050	–	–	1.6*	1.1	23**	28	1,470	1,171
Schöchl et al. [21], 2011	681	–	–	23**	32	–	–	7.5*	10.1	–	–
Chapman et al. [22], 2011	31	995**	1,800	9.9*	10.8	15*	5	23.1**	0	1,797	521
Younis et al. [23], 2018	183	–	–	3*	1	1.7**	1.1	27**	18	–	–
Joseph et al. [24], 2016	81	285**	490	4*	5	11.1*	7.4	22.3*	27.8	1,871	1,295

* $p < 0.05$; ** $p > 0.05$.

min with PCC vs. 94 min with rFVIIa; $p = 0.016$) following spleen trauma. Peak thrombin generation was greater in the PCC group than in the factor VIIa group by a median of 60.7 nM ($p = 0.008$).

In a porcine model of liver laceration, Mitterlechner et al. [19] concluded that the group who received 4-PCC demonstrated increased survival and more durable clot strength. PCC administration resulted in decreased bleeding as compared to the rFVIIa arm, although both improved ROTEM clot strength to a similar extent.

Critical Analysis

As a result, several clinical trials conducted to assess critical facts about rFVIIa in COT failed to meet the desired endpoints, thus failing to get FDA approval for trauma [5]. Our included studies suggest a statistically significant reduction in INR correction time, mortality rates, and cost of treatment with PCC compared to rFVII. Over time, the trend inclined towards the use of FFP and PCC groups rather than rFVIIa considering the above factors.

With the introduction of drugs in the management of traumatic coagulopathy, the advancement curve on this topic has risen more steeply. rFVIIa, although very promising in the beginning, has lagged far behind concerning its efficacy, safety, cost-effectiveness, and dosing regimen schedule [6], as also shown above compared to the newer PCC and the conventional FFP. This has led to a comparison between the outcomes of FFP with 3-PCC and the much later introduced 4-PCC; evaluation of several studies highlighting the critical aspect is as follows.

3-PCC +/– FFP versus FFP Alone

FFP has long been used in the management of traumatic hemorrhage and associated coagulopathy due to its dual action, that is, substitution of coagulation factors lost during hemorrhage and expansion of blood volume as these patients are volume-depleted and mostly hemodynamically unstable. Since the advent of PCC, the trends are showing an ever-increasing inclination towards their use alone or in combination with FFP in the management of COT.

Table 2 summarizes the human clinical trials conducted for comparison of 3-PCC and FFP, and their primary and secondary outcomes.

Joseph et al. [20] presented a comparative analysis of PCC and FFP. They concluded that 3-PCC + FFP was associated with an enhanced rate of INR correction ($p = 0.001$), reduced number of packed RBC ($p = 0.001$) and FFP being transfused ($p = 0.01$), a drop in mortality rate ($p = 0.04$), but a slightly higher rate of TE complications ($p < 0.05$). PCC + FFP use was associated with a higher cost of therapy ($p = 0.01$) but lower overall cost of transfusion ($p = 0.01$) in contrast to FFP alone.

Schöchl et al. [21] also established similar results with a reduced number of patients receiving packed RBC transfusion ($p = 0.001$) and platelet transfusion ($p = 0.001$) with fibrinogen + PCC compared to FFP only. However, no significant difference in hospital LOS ($p > 0.05$) or mortality rate existed ($p = 0.69$).

For trauma patients who were previously on warfarin, Chapman et al. [22] published that the time to correction of INR was lower in patients who received PCC in contrast to those who were on standardized therapies (FFP and vitamin K; $p = 0.048$), but with higher cost of therapy. Nonetheless, there was no statistically significant difference in ICU and hospital LOS, mortality rate, and TE complications between the 2 groups.

A retrospective analysis of 8 years by Younis et al. [23], on coagulopathy reversal in emergency general surgery patients presented at a single institution, demonstrated that PCC alone

or in combination with FFP results in an enhanced rate of INR correction than FFP alone ($p < 0.0001$). However, there was no statistically significant difference in TE complications ($p = 0.24$), cardiac ischemia ($p = 0.24$), hospital LOS ($p = 0.98$), intra-/postoperative bleeding ($p = 0.98$), and reoperation for bleeding ($p = 0.72$) between the 3 groups. Although the LOS in ICU was greater in patients receiving 3-PCC + FFP versus FFP alone ($p = 0.02$).

The results of these studies were divergent from those of a study conducted by Joseph et al. [24] on trauma patients who had high velocity pelvic and extremity fractures. They reported that patients receiving PCC had a lower requirement for blood products ($p = 0.02$) and lower total cost of transfusion ($p = 0.0001$) in comparison to patients receiving FFP.

The concern about PCC being more efficient alone or in combination with FFP has been highlighted by Moe et al. [25], who reported that neither 3-PCC nor 4-PCC were able to correct COT and resulted in the development of consumptive coagulopathy demonstrated by derangement of PT, PTT, fibrinogen levels, and platelet count. Also, both therapies failed to correct COT in a porcine hemorrhagic trauma model. In comparison of the 3-PCC and control groups, PT was 21.9 ± 14.6 versus 63.4 ± 43.6 s, PTT was 21.8 ± 7.2 versus 148.6 ± 87.8 s, and platelet count was 198.8 ± 75.9 versus 108.0 ± 83.7 × 10^3/μL (with $p < 0.05$ in all the parameters). The development of consumptive coagulopathy was postulated due to the decreased levels of fibrinogen, because PCC contains vitamin K-dependent coagulation factors, which require plasma or fibrinogen to complete the coagulation cascade. None of the animals with normal levels of fibrinogen ($n > 139$) developed consumptive coagulopathy following PCC administration, while 100% of animals with decreased levels of fibrinogen ($n = 9$) developed consumptive coagulopathy following PCC administration.

Kuckelman et al. [26], in a porcine hemorrhagic model, also demonstrated that the group with FFP containing concentrates of coagulation factors showed increased fibrinogen levels ($p = 0.001$), decreased lactate levels ($p = 0.039$), and shorter clotting time ($p = 0.04$) compared to non-FFP-containing groups. The multifactorial nature of traumatic coagulopathy suggests the use of both FFP and factor replacement as prime management.

Dickneite and Pragst [27], in a clinical trial on porcine hemorrhagic model in 2009, reported that administration of PCC alone resulted in accelerated hemostasis ($p = 0.003$) and reduced volume of blood loss ($p = 0.006$) in comparison to FFP alone following bone injury. This difference in the above studies may be due to the nonavailability of species-specific coagulation factor-deficient plasma since human coagulation factor-deficient plasma was used in the porcine model.

Critical Analysis

Most of the clinical trials demonstrated rapid correction of INR and reduction of hospital LOS and mortality rate in the 3-PCC group; however, the cost of therapy was higher. It can be derived that 3-PCC is practically a superior therapy for COT than FFP.

Comparison of 4-PCC +/– FFP and FFP Alone

Four-PCC has been a newer addition in the PCC family. Therefore, the available number of comparative studies with FFP are relatively fewer than with 3-PCC. Table 3 summarizes the studies conducted for comparison of 4-PCC and FFP, and their primary and secondary outcomes.

Jehan et al. [28], in a large multi-institutional retrospective analysis of ACS-TQIP database, compared the use of 4-PCC + FFP in contrast to FFP alone in trauma patients. Their results concluded that PCC + FFP causes accelerated correction of INR ($p = 0.001$), decreased requirement for packed RBC ($p = 0.04$) and FFP unit ($p = 0.03$) transfusion, lower mortality

Table 3. Comparison of 4-PCC + FFP and FFP alone

Clinical study	Sample size, *n*	Effective hemostasis, *n* (%)		INR correction time, min		Mortality rate, %		TE complications, %	
		4-PCC	FFP	4-PCC	FFP	4-PCC	FFP	4-PCC	FFP
Jehan et al. [28], 2018	120	38* (95)	74 (92)	373*	955	25*	33	2.5**	1.2
Goldstein et al. [29], 2015	181	78* (90)	61 (75)	–	–	3.4**	8	7**	8

* $p < 0.05$; ** $p > 0.05$.

Table 4. Comparison of 3-PCC and 4-PCC

Study	Sample size, *n*	Goal: correction of coagulopathy, %		Duration of hospitalization, days		TE complications, %		Mortality, %		Cost, USD	
		4-PCC	3-PCC	4-PCC	3-PCC	4-PCC	3-PCC	4-PCC	3-PCC	4-PCC	3-PCC
Zeeshan et al. [34], 2019	250	96*	94	5*	6	2.4*	2.1	26*	28	2,853	2,114
Mangram et al. [35], 2016	64	50**	83	–	–	0*	15	–	–	3,797	5,382
Voils et al. [36], 2015	165	84*	80	–	–	3*	7	9**	31	–	
Jones et al. [37], 2016	72	92.1*	84.2	10.5**	6.2	–	–	42.1*	13	–	

* $p < 0.05$; ** $p > 0.05$.

rate (p = 0.04), and lower hospital LOS (p = 0.03). However, there was no statistically significant difference between TE complications, platelet transfusion, and ICU LOS.

Goldstein et al. [29] performed a multicenter, open-label, phase 3b, randomized clinical trial for assessing the efficacy of 4-PCC versus FFP for vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions. Their study concluded that 4-PCC was better than FFP alone in achieving effective hemostasis (p = 0.014) and rapid INR correction (p = 0.001). However, there was no statistically significant difference between TE complications (p = 0.77), mortality rate (p = 0.21), and number of patients receiving RBC transfusion (p = 0.83). They also concluded that there was a significant difference in fluid overload development between the 2 groups (p = 0.04).

Critical Analysis

Along with the effects of the factors described above, the main benefits of PCC over FFP are the following: PCC is not associated with volume overload as it is administered in a single injectable form. Because of 25 times higher concentration of coagulation factors than that of human plasma, it also results in decreased time for transfusion to be done [30, 31]. PCC does not require blood grouping or thawing and can be easily preserved at room temperature. In terms of safety profile, PCC offers a massive advantage as it has undergone multiple steps for viral inactivation during the manufacturing process [32]. The grave consequence of transfusion-related acute lung injury, one of the major causes of death after transfusion, has been reduced to 0% by PCC because the antibodies responsible for causing transfusion-related acute lung injury are classically eliminated during the engineering process [32, 33].

Comparison of 3-PCC and 4-PCC

Considering the results of the studies described above which shift the balance in favor of the use of PCC in COT, the argument for choosing 4-PCC over 3-PCC still arises in its early stages. The results of studies conducted for their comparison are described as follows and summarized in Table 4.

Zeeshan et al. [34] compared the efficacy and safety of 4-PCC versus 3-PCC in the management of traumatic coagulopathy. They concluded that 4-PCC in comparison to 3-PCC administration resulted in accelerated correction of INR (p = 0.01) and decreased number of packed RBC (p = 0.04) and FFP units (p = 0.03) being transfused. No statistically significant difference between number of platelet transfusions, TE complications, mortality, hospital and ICU LOS, and total hospital cost was found between the 2 groups; 4-PCC was associated with higher cost of PCC therapy but lower cost of transfusion over-all.

For trauma patients requiring reversal of oral anticoagulants, Mangram et al. [35] proved that 4-PCC was associated with successful reversal of INR in comparison to 3-PCC (p = 0.001), with cost difference also favoring the 4-PCC group. The study revealed no difference in TE complications between the 2 groups. The timing to reversal of INR in hemorrhagic patients previously on warfarin is equally critical in reducing progression and mortality.

Voils et al. [36] established that 4-PCC is more efficient than 3-PCC in the reduction of INR to 1.5 or less within 1 h in patients on warfarin who are either bleeding or undergoing surgery or invasive procedures. For correction of iatrogenic (warfarin-induced) coagulopathy, both forms of PCC are effective, but 4-PCC proved more efficient in terms of improving mortality compared to 3-PCC (OR 0.19; p = 0.002). The authors presented this finding in a single-center retrospective trial while stating no difference in the safety profiles between the 2 groups.

Jones et al. [37], in their retrospective analysis, demonstrated a better rate of INR correction with 4-PCC compared to 3-PCC, when baseline INR levels were higher than 4.0 ($p < 0.05$). They also presented reduced hospital LOC ($p > 0.05$) and greater reduction in mortality rate ($p < 0.05$) in the 4-PCC group.

Contrary to this, in a porcine trauma model, Moe et al. [25] described that 3-PCC and 4-PCC both failed to correct COT in comparison to control. In comparison of the 4-PCC and control groups, PT was 40.3 ± 33.4 versus 16.1 ± 3.0 s, PTT was 148.6 ± 87.8 versus 51.7 ± 58.2 s, and platelet count was 170.0 ± 109.6 versus 301.7 ± 106.4 × 10^3/μL (all $p < 0.05$). The difference between the animal and porcine model may be attributed to multiple factors. These include type of fluid administered, timing of fluid resuscitation, and the physiological derangements between the 2 species.

Critical Analysis

Although the difference in chemistry between 3-PCC and 4-PCC is not significant, a review of clinical studies indicates a far superior role of 4-PCC in the management of COT and in reducing the burden of mortality as well as the cost of management. Also, considering the clinical outcomes of both treatment modalities, much needs to be done to assess the critical points more efficiently.

Conclusion

The burden of disease created by COT and its disastrous consequences on the health care system can be and have been controlled by recombinant drugs and blood products. However, the superiority of one agent over another has been a matter of intense debate since their advent. The major dimensions of an effective agent are more efficacy, better safety profile, cost-effectiveness, refined dosing regimen and schedule, and ease of administration. PCC is a relatively new addition to this family but has comprehensively surpassed the other available agents (FFP and rFVIIa) in all the qualities described above, while still awaiting FDA approval for its use in traumatic coagulopathy. No significant superiority of 4-PCC over 3-PCC can be ascertained as a difference in results of comparison is presented by different studies. However, 4-PCC has shown greater promise as a treatment modality with lesser complication risk and should be studied in detail.

The literature regarding PCC needs further attention from the observers as it has a huge influence on COT, which is an indicator of worse outcomes in patients with traumatic hemorrhage [3, 38]. There has been limited data available for PCC versus FFP and rFVIIa on particular types of injury except for traumatic brain injury. This warrants new clinical trials and prospective studies focusing on the type of injury, particularly solid organ and extremity injuries and the comparable use of these products. The parameters measuring the effectiveness of PCC also need to be standardized further to avoid any bias in future clinical trials.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

The contribution of each author is as follows. Conception of the idea: Dr. Muhammad Osama. Conception of the design of the work: Dr. Muhammad Osama and Dr. Sohaib Hasan Syed. Construction of the search strategy and review of the literature: Dr. Muhammad Osama, Dr. Sohaib Hasan Syed, and Dr. H.M. Saad Abdul Nasir. Acquisition and interpretation of data: Dr. Muhammad Osama, Dr. Sohaib Hasan Syed, Dr. Syeda Ramsha Zaidi, and Dr. H.M. Saad Abdul Nasir. Drafting the work and writing the manuscript: Dr. Muhammad Osama, Dr. Sohaib Hasan Syed, and Dr. Syeda Ramsha Zaidi. Final approval of the version to be published: Dr. Muhammad Osama.

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